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- (71) Applicant: GENENTECH, INC. [US/US]; 460 Point San Bruno Boulevard, South San Francisco, CA 94080-4990 (US).
- (72) Inventors: LAZARUS, Robert, A.; 237 Hillcrest Boulevard, Millbrae, CA 94030 (US). SHAK, Steven; 1133 Cambridge Road, Burlingame, CA 94010 (US). ULMER, Jana, S.; 346 Keystone Court, San Rafael, CA 94903 (US).
- (74) Agents: JOHNSTON, Sean, A. et al.; Genentech, Inc., 460
 Point San Bruno Boulevard, South San Francisco, CA
 94080-4990 (US).

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(54) Title: HUMAN DNASE I VARIANTS

(57) Abstract

The present invention relates to amino acid sequence variants of human DNase I that have reduced binding affinity for actin. The invention provides nucleic acid sequences encoding such actin-resistant variants, thereby enabling the production of these variants in variants of human DNase I.

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HUMAN DNASE I VARIANTS

Field of the Invention

The present invention is related to results obtained from research on human deoxyribonuclease I (DNase I), a phosphodiesterase that is capable of hydrolyzing polydeoxyribonucleic acid. It relates generally to modified (variant) forms of human DNase I and their preparation by recombinant DNA methods, to pharmaceutical compositions by which their utility can be exploited clinically, and to methods of using these DNase I variants and compositions thereof.

Background of the Invention

DNase I is a phosphodiesterase capable of hydrolyzing polydeoxyribonucleic acid. DNase I has been purified from various species to various degrees.

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Bovine DNase I has been extensively studied biochemically. See e.g., Moore, in <u>The Enzymes</u> (Boyer, P.D., ed), pp. 281-296, Academic press, New York (1981). The complete amino acid sequence for bovine DNase I is known (Liao, et al., J. Biol. Chem. <u>248</u>:1489-1495 (1973); Oefner, et al., J. Mol. Biol. <u>192</u>:605-632 (1986); Lahm, et al., J. Mol. Biol. <u>221</u>:645-667 (1991)), and DNA encoding bovine DNase I has been cloned and expressed (Worrall, et al., J. Biol. Chem <u>265</u>:21889-21895 (1990)). The structure of bovine DNase I has been determined by X-ray crystallography. Suck, et al., EMBO J. <u>3</u>:2423-2430 (1984); Suck, et al., Nature <u>321</u>:620-625 (1986); Oefner, et al., J. Mol. Biol. <u>192</u>:605-632 (1986).

DNA encoding human DNase I has been isolated and sequenced and that DNA has been expressed in recombinant host cells, thereby enabling the production of human DNase I in commercially useful quantities. Shak, et al., Proc. Nat. Acad. Sci. <u>87</u>:9188-9192 (1990).

DNase I has a number of known utilities and has been used for therapeutic purposes. Its principal therapeutic use has been to reduce the viscoelasticity of pulmonary secretions (mucus) in such diseases as pneumonia and cystic fibrosis (CF), thereby aiding in the clearing of respiratory airways. See e.g., Lourenco, et al., Arch. Intern. Med. 142:2299-2308 (1982); Shak, et al., Proc. Nat. Acad. Sci. 87:9188-9192 (1990), Hubbard, et al., New Engl. J. Med. 326:812-815 (1992); Fuchs, et al., New Engl. J. Med. 331:637-642 (1994); Bryson, et al., Drugs 48:894-906 (1994). Mucus also contributes to the morbidity of chronic bronchitis, asthmatic bronchitis, bronchiectasis, emphysema, acute and chronic sinusitis, and even the common cold.

The pulmonary secretions of persons having such diseases are complex materials, that include mucus glycoproteins, mucopolysaccharides, proteases, actin, and DNA. Some of the materials in pulmonary secretions are released from leukocytes (neutrophils) that infiltrate pulmonary tissue in response to the presence of microbes (e.g., strains of Pseudomonas, Pneumococcus, or Staphylococcus bacteria) or other irritants (e.g., tobacco smoke, pollen). In the course of reacting with such microbes or irritants, the leukocytes may degenerate and release their contents, which contribute to the viscoelasticity of the pulmonary secretions.

The ability of DNase I to reduce the viscoelasticity of pulmonary secretions has been ascribed to its enzymatic degradation of the large amounts of DNA released by neutrophils. Shak, et al., Proc. Nat. Acad. Sci. 87:9188-9192 (1990); Aitken, et al., J. Am. Med. Assoc. 267:1947-1951 (1992).

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More recently, a different mechanism has been proposed for the mucolytic effect of DNase I, involving disaggregation of actin. Vasconcellos, et al., Science 263:969-971 (1994). Actin is one of the most abundant proteins in eukaryotic cells (for example, actin comprises about 10% of total leukocyte protein) and has been extensively studied. Kabsch, et al., Ann. Rev. Biophys. Biomol. Struct 21:49-76 (1992); Sheterline, et al., Prot. Profile 1:1-121 (1994). Actin exists in two forms, a monomeric form (G-actin), and a filamentous form (F-actin) that is assembled from G-actin monomers. Polymeric filaments of actin are highly viscoelastic and contribute significantly to the viscosity of pulmonary secretions. Momet, et al., Proc. Nat. Acad. Sci. 81:3680-3684 (1984); Newman, et al., Biochemistry 24:1538-1544 (1985); Janmey, et al., Biochemistry 27:8218-8226 (1988). Vasconcellos, et al., Science 263:969-971 (1994).

Because DNase I is known to bind to actin (Lazarides, et al., Proc. Nat. Acad. Sci. 71:4742-4746 (1974); Kabsch, et al., Nature 347:37-44 (1990)) and to depolymerize actin filaments (as well as inhibit polymerization of G-actin into filaments) (Mannherz, et al., FEBS Lett. 60:34-38 (1975); Hitchcock, et al., Cell 7:531-542 (1976), Pinder, et al., Biochemistry 21:4886-4890 (1982); Weber, et al., Biochemistry 33:4780-4786 (1994)), it has been suggested that the mucolytic effect of DNase I on sputum and other pulmonary secretions is due to actin disaggregation (depolymerization) rather than to DNA hydrolysis. Vasconcellos, et al., Science 263:969-971 (1994). Consistent with this view, it is known that in the presence of actin, the DNA-hydrolytic activity of DNase I is inhibited. Lazarides, et al., Proc. Nat. Acad. Sci. 71:4742-4746 (1974); Mannherz, et al., Eur. J. Biochem 104:367-379 (1980). Also consistent with this view, it has been reported that actin severing proteins (e.g., gelsolin) are effective in decreasing the viscoelasticity of cystic fibrosis sputum. Vasconcellos, et al., Science 263:969-971 (1994); Stossel, et al., PCT Patent Publication No. WO 94/22465 (published October 13, 1994).

The present invention is based in part on research by the inventors to determine the biochemical basis of the mucolytic activity of DNase I. This research involved the design and synthesis of various human DNase I variants, and the assay of these variants to assess their ability to hydrolyze DNA, to bind to actin, and to reduce the viscoelasticity of sputum in vitro. The inventors created several classes of human DNase I variants. One class of variants (actin-resistant variants) has decreased ability to bind actin, but still has mucolytic activity and in some cases had increased mucolytic activity as compared to native human DNase I. These actin-resistant variants have about the same DNA-hydrolytic activity as native human DNase I, but such activity is less susceptible to inhibition by actin. A second class of variants bind actin with an affinity similar to that found for native human DNase I, but have decreased mucolytic activity and decreased DNA-hydrolytic activity as compared to native human DNase I.

These results indicate that the therapeutic efficacy of human DNase I in reducing the viscoelasticity of pulmonary secretions is due to its catalytic, DNA-hydrolytic activity, rather than to its ability to depolymerize filamentous actin. Accordingly, variants of human DNase I that bind actin with lower affinity than native human DNase I, but that still possess DNA-hydrolytic activity should be useful therapeutic agents, especially in the treatment of patients having pulmonary secretions that comprise relatively large amounts of actin Because such variants have reduced affinity for actin, their DNA hydrolytic activity is less inhibited in the

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presence of actin, and so these variants have greater mucolytic activity in the presence of actin, as compared to native human DNase I.

It is therefore an object of the present invention to provide human DNase I variants that possess DNA-hydrolytic activity, but bind actin with lower affinity than native human DNase I.

It is another object of the invention to provide nucleic acids encoding such actin-resistant variants of human DNase I, recombinant vectors comprising such nucleic acids, recombinant host cells transformed with those nucleic acids or vectors, and processes for producing the human DNase I variants by means of recombinant DNA technology.

The invention also is directed to pharmaceutical compositions comprising the human DNase I actinresistant variants, optionally together with a pharmaceutically acceptable excipient.

The invention also is directed to a method for reducing the viscoelasticity or viscous consistency of DNA-containing material in a patient, comprising administering a therapeutically effective dose of an actin-resistant variant of DNase I to the patient.

The invention is particularly directed to a method of treating a patient having a disease such as cystic fibrosis, chronic bronchitis, pneumonia, bronchiectasis, emphysema, asthma, or systemic lupus crythematosus, that comprises administering a therapeutically effective amount of an actin-resistant variant of DNase I to the patient.

The invention also is directed to the use of actin-resistant variants of human DNase I in in vitro diagnostic assays of a viscous material (e.g., sputum) from a patient, to measure the amount of actin present and determine whether the patient is an appropriate candidate for treatment with an actin-resistant DNase I variant.

These and other objects of the invention will be apparent to the ordinary artisan upon consideration of the specification as a whole.

Brief Description of the Figures

Figure 1 shows the amino acid sequence of human mature DNase I (SEQ. ID. NO: 1). The numbers indicate the sequential position of amino acid residues within the sequence.

Figures 2-6 show data for the following variants:

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	The state of the s			
A114C	(SEQ. ID. NO: 68)	D53R	(SEO	ID. NO: 13)
A114B	(SEQ. ID. NO: 69)			
A114G				ID. NO: 14)
A114H		D58 T	(SEQ.	ID. NO: 80)
		R13A	(SEQ.	ID. NO: 2)
	(SEQ. ID. NO: 72)	E13H		ID. NO: 3)
A114L	(SEQ. ID. NO: 73)	#13p		
A114M				ID. NO: 4)
A1140		E13W	(SEQ.	ID. NO: 51
-		E13Y	(SEQ.	ID. NO: 61
	(SEQ. ID. NO: 76)	E 69A		ID. NO: 65)
A114W	(SEQ. ID. NO: 77)	P60C		
A114Y				ID. NO: 66)
D53A		K69K	(SEQ.	ID. NO: 21)
		E 69 M	(SEQ.	ID. NO: 67)
D23C	(SEQ. ID. NO: 43)	E69 R		ID. NO: 22)
D53K	(SEQ. ID. NO: 12)			
D53L				ID. NO: 35)
D5.3M		G491	(SEQ.	ID. NO: 36)
23311	(3EQ. ID. NO: 45)	G4 9 K	(SEQ.	ID. NO: 37)
	A114B A114G A114H A114K A114L A114M A114Q A114R A114W A114Y D53A D53C D53K	A114C (SEQ. ID. NO: 68) A114B (SEQ. ID. NO: 69) A114G (SEQ. ID. NO: 70) A114H (SEQ. ID. NO: 71) A114K (SEQ. ID. NO: 72) A114L (SEQ. ID. NO: 73) A114M (SEQ. ID. NO: 74) A114Q (SEQ. ID. NO: 75) A114R (SEQ. ID. NO: 76) A114W (SEQ. ID. NO: 76) A114W (SEQ. ID. NO: 77) A114Y (SEQ. ID. NO: 78) D53A (SEQ. ID. NO: 11) D53C (SEQ. ID. NO: 43) D53K (SEQ. ID. NO: 12) D53L (SEQ. ID. NO: 44)	A114C (SEQ. ID. NO: 68) D53R A114B (SEQ. ID. NO: 69) D53Y A114G (SEQ. ID. NO: 70) D58T A114H (SEQ. ID. NO: 71) E13A A114K (SEQ. ID. NO: 72) E13H A114L (SEQ. ID. NO: 73) E13R A114M (SEQ. ID. NO: 74) E13W A114Q (SEQ. ID. NO: 75) E13Y A114R (SEQ. ID. NO: 75) E13Y A114R (SEQ. ID. NO: 76) E69A A114W (SEQ. ID. NO: 77) E69C A114Y (SEQ. ID. NO: 78) E69K D53A (SEQ. ID. NO: 11) E69M D53C (SEQ. ID. NO: 43) E69R D53K (SEQ. ID. NO: 12) G49C D53M (SEQ. ID. NO: 44) G49I	A114C (SEQ. ID. NO: 68) D53R (SEQ. A114B (SEQ. ID. NO: 69) D53Y (SEQ. A114G (SEQ. ID. NO: 70) D5BT (SEQ. A114H (SEQ. ID. NO: 71) R13A (SEQ. A114H (SEQ. ID. NO: 72) R13H (SEQ. A114L (SEQ. ID. NO: 72) R13H (SEQ. A114L (SEQ. ID. NO: 73) R13R (SEQ. A114L (SEQ. ID. NO: 73) R13R (SEQ. A114M (SEQ. ID. NO: 74) R13W (SEQ. A114Q (SEQ. ID. NO: 74) R13W (SEQ. A114Q (SEQ. ID. NO: 75) R13Y (SEQ. A114R (SEQ. ID. NO: 76) R69A (SEQ. A114W (SEQ. ID. NO: 76) R69A (SEQ. A114W (SEQ. ID. NO: 77) R69C (SEQ. A114Y (SEQ. ID. NO: 78) R69K (SEQ. D53A (SEQ. ID. NO: 11) R69M (SEQ. D53C (SEQ. ID. NO: 43) R69R (SEQ. D53L (SEQ. ID. NO: 12) G49C (SEQ. D53L (SEQ. ID. NO: 44) G49I (SEQ. D53M (SEQ. ID. NO: 44)

		1570 ID NO. 38)	V67A	(SEC.	ID.	NO	18)
	G49R	(SEQ. ID. NO: 38) (SEO. ID. NO: 39)		(SEQ.		NO	55)
	G49Y	(SEQ. ID. NO: 39) (SEQ. ID. NO: 7)	7 7 7	(SEQ.		: C N	56)
	H44A	(SEQ. ID. NO: 28)		(SEQ.		NO:	19)
	H44C	(SEQ. ID. NO: 8)		(SEQ.	ID.		
5	H44D H44E	(SEO, ID. NO: 86)		(SEC.	ID.	NC:	201
	H44N	(SEQ. ID. NO: 79)		(SEQ.	ID.	NC:	58;
	H44Q	(SEQ. ID. NO: 29)	V67P	(SEQ.	ID.	NO:	59)
	H44W	(SEQ. ID. NO: 10)	V67R	(SEQ.	ID.	NO:	60)
1.0	H44Y	(SEQ. ID. NO: 9)	V678	(SEQ.	ID.	NO:	61)
10	L45C	(SEQ. ID. NO: 30)	Y65A	(SEQ.	ID.	NO:	15)
	L45K	(SEQ. ID. NO: 31)	Y65C	(SEQ.	ID.	NC:	51)
	L45R	(SEQ. ID. NO: 32)	Y65E	(SEQ.	ID.	NC:	87)
	L52C	(SEQ. ID. NO: 40)	Y65K	(SEQ.	ID.	11 C++	52)
15	L52K	(SEQ. ID. NO: 41)	Y65M	(SEQ.		NC:	
	L52M	(SEQ. ID. NO: 42)	Y65P	(SEQ.			97)
	L52N	(SEQ. ID. NO: 90)	Y65R	(SEQ		NO.	
	L52R	(SEQ. ID. NO: 91)	Y65S	(SEQ.		NO:	
	N56C	(SEQ. ID. NO: 46)	¥65W	(SEQ.			17)
20	N56C	(SEQ. ID. NO: 92)	D53R:E69R				25)
	N56F	(SEQ. ID. NO: 47)	D53R:H44A				23)
	N56F	(SEQ. ID. NO: 93)	D53R:Y65A				
	N56K	(SEQ. ID. NO: 94)	H64N:V66T				
	N56K	(SEQ. ID. NO: 48)	S68N: P70T	(SEQ.		N D:	
25	N56R	(SEQ. ID. NO: 49)	594N:Y96T	(SEQ		: CN	
	N56R	(SEQ. ID. NO: 95)	V67N: E69T	(SEQ			
	N56W	(SEQ. ID. NO: 50)	Y65N:V67T				
	N56W	(SEQ. ID. NO: 96)	D53R:Y65A:	E 69R	(SEQ.	. ID	NO:
	S68K	(SEQ. ID. NO: 62)	88)				110
30	S68M	(SEQ. ID. NO: 63)	H44A:D53R	:Y65A	(SEÇ	. 10	NO:
	368 R	(SEQ. ID. NO: 64)	26)				
	V48C	(SEQ. ID. NO: 33)	H44A: Y65A	:E69R	(SEQ	. 10	. NU:
	V48K	(SEQ. ID. NO: 34)	27)				
	V48R	(SEQ. ID. NO: 89)					
35	V66N	(SEQ. ID. NO: 83)					

Figures 2A-D show the relative specific activity of native human DNase I and variants. The error bars represent the standard deviation (n-weighted). The relative specific activity of Pulmozyme& human DNase I (Genentech, Inc., South San Francisco, California USA) is defined as 1.0. The relative specific activity of native human DNase I is greater than that of Pulmozyme® due to the occurrence in Pulmozyme® of a deamidated form of human DNase I that has reduced DNA-hydrolytic activity (Frenz, et al., PCT Patent Publication No WO 93/25670, published December 23, 1993).

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Figure 3 shows the DNA-hydrolytic activity of native human DNase I and single-residue variants of human DNase I in the presence of actin, as determined in a hyperchromicity assay. "Percent activity" is the percent DNA-hydrolytic activity of the DNase I (native or variant) calculated as described in Example 3: the DNA-hydrolytic activity of the DNase I in the absence of actin is defined as 100 percent activity. The error bars represent the standard deviation.

Figure 4 shows the DNA-hydrolytic activity of native human DNase I and multiple-residue variants of human DNase I in the presence of actin, as determined in a hyperchromicity assay or a methyl green assay. "Percent activity" is the percent DNA-hydrolytic activity of the DNase I (native or variant) calculated as described in Example 3; the DNA-hydrolytic activity of the DNase I in the absence of actin is defined as 100 percent activity. The error bars represent the standard deviation

Figures 5A-D show the relative binding affinity of human DNase I variants for actin as determined in an actin binding ELISA assay (as described in Example 3). The EC₅₀ value is the concentration of the DNase I (native or variant) that is required to give a half-maximal signal in the assay. The error bars represent the standard deviation. The EC₅₀ values for Pulmozyme® and native human DNase I are 67 ± 23 pM (n = 31) and 87 ± 14 pM (n = 32), respectively. The relative binding affinity shown in the figure is the EC₅₀ value determined for the human DNase I variant divided by the EC₅₀ value determined for native human DNase I. Variants where the EC₅₀ value was larger than could be measured in the assay are indicated as having a ratio (EC₅₀ (DNase) variant)/EC₅₀ (native DNase I)) greater than a certain value (for example, >10, >100, >300, >2000, >20,000, >35,000).

Figure 6 shows the mucolytic activity of native human DNase I and variants of human DNase I in sputum samples from cystic fibrosis patients, as determined by a compaction assay. The error bars represent the standard error of the mean.

Figure 7 shows a schematic representation of the actin binding ELISA assay described in Example 3

Detailed Description

20 I. <u>Definitions</u>

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As used herein, the terms "human DNase I", "native human DNase I", and "wild-type DNase I" refer to the polypeptide having the amino acid sequence of human mature DNase I set forth in Figure 1.

A "variant" or "amino acid sequence variant" of human DNase I is a polypeptide that comprises an amino acid sequence different from that of native human DNase I. Generally, a variant will possess at least 80% sequence identity (homology), preferably at least 90% sequence identity, more preferably at least 95% sequence identity, and most preferably at least 98% sequence identity with native human DNase I. Percentage sequence identity is determined, for example, by the Fitch, et al., Proc. Nat. Acad. Sci. USA 80:1382-1386 (1983), version of the algorithm described by Needleman, et al., J. Mol. Biol. 48:443-453 (1970), after aligning the sequences to provide for maximum homology

The terms "human DNase I actin-resistant variant", "actin-resistant variant", and "actin-resistant variant of human DNase I" refer to a variant of native human DNase I that has (1) DNA-hydrolytic activity and (2) reduced binding affinity for actin.

"DNA-hydrolytic activity" refers to the enzymatic activity of native human DNase I or a variant of human DNase I in hydrolyzing (cleaving) substrate DNA to yield 5'-phosphorylated oligonucleotide end products. DNA-hydrolytic activity is readily determined by any of several different methods known in the art, including analytical polyacrylamide and agarose gel electrophoresis, hyperchromicity assay (Kunitz, J. Gen.

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Physiol. 33:349-362 (1950); Kunitz, J. Gen. Physiol. 33:363-377 (1950)), or methyl green assay (Kurnick Arch. Biochem. 29:41-53 (1950); Sinicropi, et al., Anal. Biochem. 222:351-358 (1994))

The "binding affinity" of native human DNase I or an actin-resistant variant of human DNase I for actin refers to the ability of the DNase I to noncovalently bind to actin. Binding affinity may be determined by any of various methods known in the art, for example, as described in Mannherz, et al., Eur. J. Biochem 104.367-379 (1980). Alternatively, the relative binding affinities of different DNases (e.g., native human DNase I and variants thereof) are determined by measuring the binding of the DNases to immobilized actin in an ELISA assay (described in Example 3), or by comparing the DNA-hydrolytic activity of the DNases in the presence and absence of actin (also described in Example 3). The methods described in the Examples are especially convenient for screening variants of human DNase I to rapidly identify those variants that have a reduced binding affinity for actin.

A human DNase I actin-resistant variant having "reduced binding affinity for actin" is one having a binding affinity for actin that is relatively less than the affinity with which native human DNase I binds actin. determined under comparable conditions. If the actin binding ELISA assay as described in Example 3 is used to determine the binding affinity of a human DNase I (native or variant) for actin, then an actin-resistant variant having "reduced binding affinity for actin" will be one having an EC₅₀ value that is greater than that of native human DNase I. In that assay, an actin-resistant variant typically will have an EC₅₀ value five-fold to 100-fold greater than that of native human DNase; but actin-resistant variants having an EC₅₀ value over 500-fold greater than that of native human DNase I also are readily produced, especially by altering multiple amino acid residues of the native human DNase I amino acid sequence (see e.g., Figure 5A, 5D).

"Mucolytic activity" refers to the reduction of viscoelasticity (viscosity) of sputum or other biological material, for example as observed upon treatment of the material with native human DNase I or a variant of human DNase I. Mucolytic activity is readily determined by any of several different methods known in the art, including sputum compaction assay (PCT Patent Publication No. WO 94/10567, published May 11, 1994), assays using a torsion pendulum (Janmey, J. Biochem. Biophys. Methods 22/41-53 (1991), or other rheological methodologies.

"Polymerase chain reaction," or "PCR," generally refers to a method for amplification of a desired nucleotide sequence in vitro, as described, for example, in U.S. Pat. No. 4,683,195. In general, the PCR method involves repeated cycles of primer extension synthesis, using oligonucleotide primers capable of hybridizing preferentially to a template nucleic acid.

"Cell," "host cell," "cell line," and "cell culture" are used interchangeably herein and all such terms should be understood to include progeny resulting from growth or culturing of a cell. "Transformation" and "transfection" are used interchangeably to refer to the process of introducing DNA into a cell.

"Operably linked" refers to the covalent joining of two or more DNA sequences, by means of enzymatic ligation or otherwise, in a configuration relative to one another such that the normal function of the sequences can be performed. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide. a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence—or

a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous and, in the case of a secretory leader, contiguous and in reading phase. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, then synthetic oligonucleotide adaptors or linkers are used, in conjunction with standard recombinant DNA methods.

Amino acids are identified herein by three-letter or single-letter designations, as follows

	Asp D aspartic acid	He I isoleucine
	Thr T threonine	Leu L leucine
	Ser S serine	Tyr Y tyrosine
10	Glu E glutamic acid	Phe F phenylalaning
	Pro P proline	His H histidine
	Gly G glycine	Lys K lysine
	Ala A alanine	Arg R arginine
	Cys C cysteine	Trp W tryptophan
15	Val V valine	Gln Q glutamine
	Met M methionine	Asn N asparagine

II. Selection of Actin-Resistant Variants

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The present invention is based upon the study of structure, actin binding properties, DNA-hydrolytic activity, and mucolytic activity of amino acid sequence variants of human DNase I. The actin-resistant variants of the present invention have DNA-hydrolytic activity, but bind actin with less affinity than native human DNase I. The reduction in actin binding preferably is achieved by making mutations at and/or around those amino acid residues within native human DNase I that appear to affect the binding of actin, including, for example, the Glu13, His44, Leu45, Val48, Gly49, Leu52, Asp53, Asn56, Asp58, His64, Tyr65, Val66, Val67, Ser68, Glu69, Pro70, Ser94, Tyr96, and Alal 14 residues of native human DNase I (the number following the three-letter amino acid designation indicates the specific position of the amino acid residue within the Figure I sequence).

There are a variety of ways in which one can make actin-resistant variants of human DNase I. In one embodiment of this invention, an actin-resistant variant is prepared by introducing either single or multiple amino acid substitutions, insertions, and/or deletions at or adjacent to (i.e., within about five amino acid residues of) those amino acid residues of native human DNase I that affect actin binding. Some illustrative examples of such mutations are as follows: D53R, D53K, D53Y, D53A, Y65A, Y65E, Y65R, V67E, V67K, E69R, D53R, Y65A, D53R: Y65A, D53R: Y65A, H44A: Y65A: E69R (see Figures 2-6).

In another embodiment of this invention, an actin-resistant variant is prepared by introducing mutation(s) that create a new glycosylation site at or adjacent to (i.e., within about five amino acid residues of) an amino acid residues of native human DNase I that affect actin binding. For example, site-directed mutagenesis is used to introduce one of the tripeptide sequences, asparagine-X-serine or asparagine-X-threonine (wherein X is any amino acid except proline), which are recognition sequences for enzymatic attachment of a

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carbohydrate moiety to the asparagine side chain. Creighton, <u>Proteins</u>, pp.76-78 (W.H. Freeman, 1984). Steric hindrance occurring between the carbohydrate moiety of the resulting N-glycosylated variant DNase I and actin can reduce or prevent actin binding and consequential inhibition of the DNase I DNA-hydrolytic activity, as compared to native human DNase I. Some illustrative examples of such mutations to introduce a new glycosylation site are as follows. H44N, D58S, D58T, V66N, H44N:T46S, H64N V66S, H64N V66T, Y65N:V67S, Y65N:V67T, V66N:S68T, V67N:E69S, V67N:E69T, S68N:P70S, S68N:P70T, S94N Y96S S94N:Y96T.

Optionally, in conjunction with such mutations to create a new glycosylation site, the naturally occurring glycosylation site at positions 18 and/or 106 within the native human DNase I amino acid sequence may be deleted, depending upon the extent of glycosylation desired in the actin-resistant variant.

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In a further embodiment of this invention, site-directed mutagenesis is used to introduce residues at or adjacent to (i.e., within about five amino acid residues of) those amino acid residues of native human DNase I that are involved in actin binding that are suitable for post-translational modification either biologically or chemically (see below). Means, et al., Chemical Modification of Proteins (Holden-Day, 1971); Glazer, et al., Chemical Modification of Proteins: Selected Methods and Analytical Procedures (Elsevier, 1975); Creighton. Proteins, pp.70-87 (W.H. Freeman, 1984); Lundblad, Chemical Reagents for Protein Modification (CRC Press 1991). Such post-translational modifications may introduce steric hinderance or altered electrostatic properties into the DNase I that will reduce or prevent actin binding and subsequent inhibition of DNA-hydrolytic activity, as compared to native human DNase I. For example, a cysteine residue may be introduced at or adjacent to a residue of native human DNase I that is involved in actin binding. The free thiol of the cysteine residue may form an intermolecular disulfide bond with another such DNase I variant to form a DNase I dimer, or may be modified, for example, with a thiol-specific alkylating agent. Some illustrative examples of such mutations are as follows: H44C, L45C, V48C, G49C, L52C, D53C, N56C, Y65C, V67C, E69C, A114C.

For convenience, substitutions, insertions, and/or deletions in the amino acid sequence of native human DNase I are usually made by introducing mutations into the corresponding nucleotide sequence of the DNA encoding native human DNase I, for example by site-directed mutagenesis. Expression of the mutated DNA then results in production of the variant human DNase I, having the desired (non-native) amino acid sequence.

Whereas any technique known in the art can be used to perform site-directed mutagenesis, e.g. as disclosed in Sambrook, et al., Molecular Cloning: A Laboratory Manual, Second Edition (Cold Spring Harbor Laboratory Press, New York (1989)), oligonucleotide-directed mutagenesis is the preferred method for preparing the human DNase I variants of this invention. This method, which is well known in the art (Zoller, et al., Meth. Enz. 100:4668-500 (1983); Zoller, et al., Meth. Enz. 154:329-350 (1987); Carter, Meth. Enz. 154:382-403 (1987); Kunkel, et al., Meth. Enzymol. 154:367-382 (1987); Horwitz, et al., Meth. Enz. 185:599-611 (1990)), is particularly suitable for making substitution variants, although it may also be used to conveniently prepare deletion and insertion variants.

The site-directed mutagenesis technique typically employs a phage vector that exists in both a single-stranded and double-stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage, and plasmid vectors that contain a single-stranded phage origin of replication (Messing, et

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al., Meth. Enzymol. 101:20-78 (1983); Veira et al., Meth. Enzymol. 153:3-11 (1987); Short, et al., Nuc. Acids Res. 16:7583-7600 (1988)). Replication of these vectors in suitable host cells results in the synthesis of single-stranded DNA that may be used for site-directed mutagenesis.

Briefly, in carrying out site-directed mutagenesis of DNA encoding native human DNase I (or a variant thereof), the DNA is altered by first hybridizing an oligonucleotide encoding the desired mutation to a single strand of the DNA. After hybridization, a DNA polymerase is used to synthesize an entire second strand, using the hybridized oligonucleotide as a primer, and using the single strand of the DNA as a template. Thus, the oligonucleotide encoding the desired mutation is incorporated in the resulting double-stranded DNA.

Oligonucleotides for use as hybridization probes or primers may be prepared by any suitable method, such as by purification of a naturally occurring DNA or by in vitro synthesis. For example, oligonucleotides are readily synthesized using various techniques in organic chemistry, such as described by Narang, et al., Meth. Enzymol. 68:90-98 (1979); Brown, et al., Meth. Enzymol. 68:109-151 (1979); Caruthers, et al., Meth. Enzymol. 154:287-313 (1985). The general approach to selecting a suitable hybridization probe or primer is well known. Keller, et al., DNA Probes, pp.11-18 (Stockton Press, 1989). Typically, the hybridization probe or primer will contain 10-25 or more nucleotides, and will include at least 5 nucleotides on either side of the sequence encoding the desired mutation so as to ensure that the oligonucleotide will hybridize preferentially at the desired location to the single-stranded DNA template molecule.

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Of course, site-directed mutagenesis may be used to introduce multiple substitution, insertion, or deletion mutations into a starting DNA. If the sites to be mutated are located close together, the mutations may be introduced simultaneously using a single oligonucleotide that encodes all of the desired mutations. If, however, the sites to be mutated are located some distance from each other (separated by more than about ten nucleotides), it is more difficult to generate a single oligonucleotide that encodes all of the desired changes. Instead, one of two alternative methods may be employed

In the first method, a separate oligonucleotide is generated for each desired mutation. The oligonucleotides are then annealed to the single-stranded template DNA simultaneously, and the second strand of DNA that is synthesized from the template will encode all of the desired amino acid substitutions

The alternative method involves two or more rounds of mutagenesis to produce the desired variant. The first round is as described for introducing a single mutation. The second round of mutagenesis utilizes the mutated DNA produced in the first round of mutagenesis as the template. Thus, this template already contains one or more mutations. The oligonucleotide encoding the additional desired amino acid substitution(s) is then annealed to this template, and the resulting strand of DNA now encodes mutations from both the first and second rounds of mutagenesis. This resultant DNA can be used as a template in a third round of mutagenesis, and so on.

PCR mutagenesis (Higuchi, in <u>PCR Protocols</u>, pp.177-183 (Academic Press, 1990): Vallette, et al., Nuc. Acids Res. <u>17</u>:723-733 (1989)) is also suitable for making the variants of human DNase I. Briefly, when small amounts of template DNA are used as starting material in a PCR, primers that differ slightly in sequence from the corresponding region in the template DNA can be used to generate relatively large quantities of a specific DNA fragment that differs from the template sequence only at the positions where the primers differ

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from the template. For introduction of a mutation into a plasmid DNA, for example, the sequence of one of the primers includes the desired mutation and is designed to hybridize to one strand of the plasmid DNA at the position of the mutation; the sequence of the other primer must be identical to a nucleotide sequence within the opposite strand of the plasmid DNA, but this sequence can be located anywhere along the plasmid DNA. It is preferred, however, that the sequence of the second primer is located within 200 nucleotides from that of the first, such that in the end the entire amplified region of DNA bounded by the primers can be easily sequenced PCR amplification using a primer pair like the one just described results in a population of DNA fragments that differ at the position of the mutation specified by the primer, and possibly at other positions, as template copying is somewhat error-prone. Wagner, et al., in PCR Topics, pp.69-71 (Springer-Verlag, 1991).

If the ratio of template to product amplified DNA is extremely low, the majority of product DNA fragments incorporate the desired mutation(s). This product DNA is used to replace the corresponding region in the plasmid that served as PCR template using standard recombinant DNA methods. Mutations at separate positions can be introduced simultaneously by either using a mutant second primer, or performing a second PCR with different mutant primers and ligating the two resulting PCR fragments simultaneously to the plasmid fragment in a three (or more)-part ligation.

Another method for preparing variants, cassette mutagenesis, is based on the technique described by Wells et al., Gene, 34:315-323 (1985). The starting material is the plasmid (or other vector) comprising the DNA sequence to be mutated. The codon(s) in the starting DNA to be mutated are identified. There must be a unique restriction endonuclease site on each side of the identified mutation site(s). If no such restriction sites exist, they may be generated using the above-described oligonucleotide-mediated mutagenesis method to introduce them at appropriate locations in the DNA. The plasmid DNA is cut at these sites to linearize it. A double-stranded oligonucleotide encoding the sequence of the DNA between the restriction sites but containing the desired mutation(s) is synthesized using standard procedures, wherein the two strands of the oligonucleotide are synthesized separately and then hybridized together using standard techniques. This double-stranded oligonucleotide is referred to as the cassette. This cassette is designed to have 5' and 3' ends that are compatible with the ends of the linearized plasmid, such that it can be directly ligated to the plasmid. The resulting plasmid contains the mutated DNA sequence.

The presence of mutation(s) in a DNA is determined by methods well known in the art, including restriction mapping and/or DNA sequencing. A preferred method for DNA sequencing is the dideoxy chain termination method of Sanger, et al., Proc. Nat. Acad. Sci. USA 72:3918-3921 (1979).

DNA encoding a human DNase I variant is inserted into a replicable vector for further cloning or expression. "Vectors" are plasmids and other DNAs that are capable of replicating within a host cell, and as such, are useful for performing two functions in conjunction with compatible host cells (a vector-host system). One function is to facilitate the cloning of the nucleic acid that encodes a human DNase I variant i.e., to produce usable quantities of the nucleic acid. The other function is to direct the expression of a human DNase I variant. One or both of these functions are performed by the vector in the particular host cell used for cloning or expression. The vectors will contain different components depending upon the function they are to perform

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To produce a human DNase I variant, an expression vector will comprise DNA encoding the variant, as described above, operably linked to a promoter and a ribosome binding site. The variant then is expressed directly in recombinant cell culture, or as a fusion with a heterologous polypeptide, preferably a signal sequence or other polypeptide having a specific cleavage site at the junction between the heterologous polypeptide and the human DNase I variant.

Prokaryotes (e.g., E. coli. and other bacteria) are the preferred host cells for the initial cloning steps of this invention. They are particularly useful for rapid production of large amounts of DNA, for production of single-stranded DNA templates used for site-directed mutagenesis, and for DNA sequencing of the variants generated. Prokaryotic host cells also may be used for expression of DNA encoding a human DNase I variant Polypeptides that are produced in prokaryotic cells typically will be non-glycosylated.

In addition, the human DNase I variants of this invention may be expressed in eukaryotic host cells, including eukaryotic microbes (e.g., yeast) or cells derived from an animal or other multicellular organism (e.g., Chinese hamster ovary cells, and other mammalian cells), or in live animals (e.g., cows, goats, sheep)

Cloning and expression methodologies are well known in the art. Examples of prokaryotic and eukaryotic host cells, and expression vectors, suitable for use in producing the human DNase I variants of the present invention are, for example, those disclosed in Shak, PCT Patent Publication No. WO 90:07572 (published July 12, 1990).

If prokaryotic cells or cells that contain substantial cell wall constructions are used as hosts, the preferred methods of transfection of the cells with DNA is the calcium treatment method described by Cohen et al., Proc. Natl. Acad. Sci. 69:2110-2114 (1972) or the polyethylene glycol method of Chung et al., Nuc. Acids. Res. 16:3580 (1988). If yeast are used as the host, transfection is generally accomplished using polyethylene glycol, as taught by Hinnen, Proc. Natl. Acad. Sci. U.S.A., 75: 1929-1933 (1978). If mammalian cells are used as host cells, transfection generally is carried out by the calcium phosphate precipitation method, Graham, et al., Virology 52:546 (1978), Gorman, et al., DNA and Protein Eng. Tech. 2:3-10 (1990). However, other known methods for introducing DNA into prokaryotic and eukaryotic cells, such as nuclear injection, electroporation, or protoplast fusion also are suitable for use in this invention.

Particularly useful in this invention are expression vectors that provide for the transient expression in mammalian cells of DNA encoding human DNase I variants. In general, transient expression involves the use of an expression vector that is able to efficiently replicate in a host cell, such that the host cell accumulates many copies of the expression vector and, in turn, synthesizes high levels of a desired polypeptide encoded by the expression vector. Transient expression systems, comprising a suitable expression vector and a host cell, allow for the convenient positive identification of polypeptides encoded by cloned DNAs, as well as for the rapid screening of such polypeptides for desired biological or physiological properties. Wong, et al., Science 228:810-815 (1985); Lee, et al., Proc. Nat Acad. Sci. USA 82:4360-4364 (1985); Yang, et al., Cell 47:3-10 (1986). Thus, transient expression systems are conveniently used for expressing the DNA encoding amino acid sequence variants of native human DNase I, in conjunction with assays to identify those variants that bind actin with lower affinity than native human DNase I as well as assays to measure those variants with DNA-hydrolytic activity

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A human DNase I variant preferably is secreted from the host cell in which it is expressed, in which case the variant is recovered from the culture medium in which the host cells are grown. In that case, it may be desirable to grow the cells in a serum free culture medium, since the absence of serum proteins and other serum components in the medium may facilitate purification of the variant. If it is not secreted, then the human DNase I variant is recovered from lysates of the host cells. When the variant is expressed in a host cell other than one of human origin, the variant will be completely free of proteins of human origin. In any event, it will be necessary to purify the variant from recombinant cell proteins in order to obtain substantially homogeneous preparations of the human DNase I variant. For therapeutic uses, the purified variant preferably will be greater than 99% pure (i.e., any other proteins will comprise less than 1% of the total protein in the purified composition).

Generally, purification of a human DNase I variant is accomplished by taking advantage of the differential physicochemical properties of the variant as compared to the contaminants with which it may be associated. For example, as a first step, the culture medium or host cell lysate is centrifuged to remove particulate cell debris. The human DNase I variant thereafter is purified from contaminant soluble proteins and polypeptides, for example, by ammonium sulfate or ethanol precipitation, gel filtration (molecular exclusion chromatography), ion-exchange chromatography, hydrophobic chromatography, immunoaffinity chromatography (e.g., using a column comprising anti-human DNase I antibodies coupled to Sepharose), tentacle cation exchange chromatography (Frenz, et al., PCT Patent Publication No. WO 93/25670, published December 23, 1993), reverse phase HPLC, and/or gel electrophoresis.

Of course, one skilled in the art will appreciate that the purification methods that are used for native human DNase I may require some modification to be useful in purifying a human DNase I variant, to account for structural and other differences between the native and variant proteins. For example, in some host cells (especially bacterial host cells) the human DNase I variant may be expressed initially in an insoluble, aggregated form (referred to in the art as "refractile bodies" or "inclusion bodies") in which case it will be necessary to solubilize and renature the human DNase I variant in the course of its purification. Methods for solubilizing and renaturing recombinant protein refractile bodies are known in the art (see e.g., Builder, et al., U.S. Patent No. 4,511,502).

In another embodiment of this invention, human DNase I variants are prepared by making covalent modifications directly in a native or variant human DNase I protein. Such modifications are made to affect actin binding or another property of the protein (e.g., stability, biological half-life, immunogenicity), and may be made instead of or in addition to the amino acid sequence substitution, insertion, and deletion mutations described above.

Covalent modifications may be introduced by reacting targeted amino acid residues of the native or variant human DNase I with an organic derivatizing agent that is capable of reacting with selected amino acid side-chains or N- or C-terminal residues. Suitable derivatizing agents and methods are well known in the art

For example, cysteinyl residues most commonly are reacted with α -haloacetates (and corresponding amines), such as chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteinyl residues also are derivatized by reaction with bromotrifluoroacetone, α -bromo- β -(5-

imidozoyl)propionic acid, chloroacetyl phosphate. N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

Histidyl residues are derivatized by reaction with diethylpyrocarbonate at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain. Para-bromophenacyl bromide also is useful, the reaction is preferably performed in 0.1M sodium cacodylate at pH 6.0.

Lysinyl and amino terminal residues are reacted with succinic or other carboxylic acid anhydrides. Derivatization with these agents has the effect of reversing the charge of the lysinyl residues. Other suitable reagents for derivatizing α -amino-containing residues include imidoesters such as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid. O-methylisourea; 2,4-pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginyl residues are modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pK_a of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

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Carboxyl side groups (aspartyl or glutamyl) are selectively modified by reaction with carbodiimides (R'-N=C=N-R'), where R and R' are different alkyl groups, such as 1-cyclohexyl-3-(2-morpholinyl-4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues are converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Covalent coupling of glycosides to amino acid residues of the protein may be used to modify or increase the number or profile of carbohydrate substituents, especially at or adjacent to those residues that are involved in actin binding. Depending on the coupling mode used, the sugar(s) may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan or (f) the amide group of glutamine. Suitable methods are described, for example in PCT Patent Publication No. WO 87/05330 (published September 11, 1987), and in Aplin, et al., CRC Crit. Rev. Biochem., pp. 259-306 (1981).

The covalent attachment of agents such as polyethylene glycol (PEG) or human serum albumin to human DNase I variants may reduce immunogenicity and/or toxicity of the variant and/or prolong its half-life, as has been observed with other proteins. Abuchowski, et al., J. Biol. Chem. 252:3582-3586 (1977); Poznansky, et al., FEBS Letters 239:18-22 (1988); Goodson, et al., Biotechnology 8:343-346 (1990); Katre, J. Immunol. 144:209-213 (1990); Harris, Polyethylene Glycol Chemistry (Plenum Press, 1992). In addition, modification of native human DNase I or a variant thereof by these agents at or adjacent to (i.e., within about five amino acid residues of) an amino acid residue that affects actin binding may result in an actin-resistant variant

In a further embodiment, a human DNase I actin-resistant variant may comprise a mutation at the Asn residue that occurs at position 74 of the native human DNase I amino acid sequence (e.g., a N74D, N74K, or

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N74S mutation), in order to reduce or prevent the deamidation of the DNase I variant. Frenz, et al., PCT Patent Publication No. WO 93/25670, published December 23, 1993. As another example, a human DNase I actin-resistant variant may comprise an amino acid sequence mutation or other covalent modification that reduces the susceptibility of the variant to degradation by proteases (e.g., neutrophil elastase) that may be present in sputum and other biological materials.

The DNA-hydrolytic activity and actin-binding affinity of the human DNase I variants prepared as described above are readily determined using assays and methods known in the art and as described herein. Any such variant having DNA-hydrolytic activity and reduced binding affinity for actin (as defined above) is an actin-resistant variant within the scope of this invention.

The human DNase I actin-resistant variants of this invention are used to reduce the viscoelasticity of DNA-containing material, such as sputum, mucus, or other pulmonary secretions. Such variants are particularly useful for the treatment of patients with pulmonary disease who have abnormal viscous or inspissated secretions and conditions such as acute or chronic bronchial pulmonary disease, including infectious pneumonia, bronchitis or tracheobronchitis, bronchiectasis, cystic fibrosis, asthma, tuberculosis, and fungal infections. For such therapies, a solution or finely divided dry preparation of the actin-resistant variant is instilled in conventional fashion into the airways (e.g., bronchi) or lungs of a patient, for example by aerosolization.

The actin-resistant variants are also useful for adjunctive treatment of abscesses or severe closed-space infections in conditions such as empyema, meningitis, abscess, peritonitis, sinusitis, otitis, periodontitis, pericarditis, pancreatitis, cholelithiasis, endocarditis and septic arthritis, as well as in topical treatments in a variety of inflammatory and infected lesions such as infected lesions of the skin and/or mucosal membranes, surgical wounds, ulcerative lesions and burns. The actin-resistant variant may improve the efficacy of antibiotics used in the treatment of such infections (e.g., gentamicin activity is markedly reduced by reversible binding to intact DNA).

Native human DNase I and actin-resistant variants thereof also may be useful for the treatment for systemic lupus erythematosus (SLE), a life-threatening autoimmune disease characterized by the production of diverse autoantibodies. DNA is a major antigenic component of the immune complexes. In this instance, the human DNase I (native or variant) may be given systemically, for example by intravenous, subcutaneous, intrathecal, or intramuscular administration to the affected patient.

Native human DNase I and actin-resistant variants thereof also may be useful for preventing the new development and/or exacerbation of respiratory infections, such as may occur in patients having cystic fibrosis, chronic bronchitis, asthma, pneumonia, or other pulmonary disease, or patients whose breathing is assisted by ventilator or other mechanical device, or other patients at risk of developing respiratory infections, for example post-surgical patients.

The actin-resistant variants can be formulated according to known methods to prepare therapeutically useful compositions. A preferred therapeutic composition is a solution of an actin-resistant variant in a buffered or unbuffered aqueous solution, and preferably is an isotonic salt solution such as 150 mM sodium chloride containing 10 mM calcium chloride at pH 7. These solutions are particularly adaptable for use in

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commercially-available nebulizers including jet nebulizers and ultrasonic nebulizers useful for administration directly into the airways or lungs of an affected patient.

In another embodiment, the therapeutic composition comprises a dry powder of the actin-resistant variant, preferably prepared by spray-drying of a solution of the actin-resistant variant, essentially as described in co-pending U.S. Patent Application Serial No. 08/206,020 (filed March 4, 1994).

In a further embodiment, the therapeutic composition comprises cells actively producing an actinresistant variant of human DNase I. Such cells may be directly introduced into the tissue of a patient, or may
be encapsulated within porous membranes which are then implanted in a patient, in either case providing for
the delivery of the actin-resistant variant into areas within the body of the patient in need of increased
concentrations of DNA-hydrolytic activity. For example, the patient's own cells could be transformed, either
in vivo or ex vivo, with DNA encoding an actin-resistant variant of human DNase I, and then used to produce
the DNase I directly within the patient.

The therapeutically effective amount of an actin-resistant human DNase I variant will depend, for example, upon the amount of DNA and actin in the material to be treated, the therapeutic objectives, the route of administration, and the condition of the patient. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. In view of its reduced binding affinity for actin and consequential increased DNA-hydrolytic activity in the presence of actin relative to native human DNase I, the amount of an actin-resistant variant required to achieve a therapeutic effect may be less than the amount of native human DNase I necessary to achieve the same effect under the same conditions. Generally, the therapeutically effective amount of the actin-resistant variant will be a dosage of from about 0.1 µg to about 5 mg of the variant per kilogram of body weight of the patient, administered within pharmaceutical compositions, as described herein.

An actin-resistant DNase I variant optionally is combined with or administered in concert with one or more other pharmacologic agents used to treat the conditions listed above, such as antibiotics, bronchodilators, anti-inflammatory agents, mucolytics (e.g. n-acetyl-cysteine), actin binding or actin severing proteins (e.g., gelsolin; Matsudaira et al., Cell 54:139-140 (1988); Stossel, et al., PCT Patent Publication No. WO 94/22465 (published October 13, 1994)), protease inhibitors, or gene therapy product (e.g., comprising the cystic fibrosis transmembrane conductance regulator (CFTR) gene, Riordan, et al., Science 245:1066-1073 (1989)).

The following examples are offered by way of illustration only and are not intended to limit the invention in any manner. All patent and literature references cited herein are expressly incorporated.

EXAMPLE 1

Mutagenesis of Human DNase I

E. coli strain CJ236 (BioRad Laboratories, Richmond, California USA) was transformed with plasmid pRK.DNase.3 using the method of Chung et al. (Nuc. Acids. Res. 16:3580 (1988). The plasmid pRK DNase.3 used in making the present invention is as described in PCT Patent Publication No. WO 90/07572 (published July 12, 1990), except that the nucleotide sequence encoding human DNase 1 is as shown in Figure 1. Transformed cells were plated on LB agar plates containing 50 μg/ml carbenicillin and grown overnight at 37°C. 2YT broth (5 ml) containing 50 μg/ml carbenicillin and 10 μl VCSM13 helper phage (Stratagene, La

Jolla, California USA) was inoculated with an individual colony from the agar plate and grown overnight at 37°C with agitation. Single stranded DNA was isolated from this culture and used as template for subsequent mutagenesis.

Site-directed mutagenesis was accomplished using synthetic oligonucleotides according to the method of Kunkel, et al. (Meth. Enzymol. 154: 367-382 (1987). The mutagenic oligonucleotides were 21-mers or 24-mers, having either 9 or 12 exact base matches 5' to the mismatched codon and 9 exact base matches 3' to the mismatched codon. Following mutagenesis, single stranded DNA from individual clones was subjected to dideoxy sequencing (Sanger, et al., Proc. Nat. Acad. Sci. USA 74: 5463-5467 (1977)). DNA having variant nucleotide sequences then was transformed as described above into E. coli strain XL1 Blue MRF' (Stratagene). After plating and single colony isolation as before, individual colonies were used to inoculate 0.5 liter LB broth containing 50 ug/ml carbenicillin. Following growth overnight with agitation at 37°C, the cells were harvested by centrifugation and the variant DNA (in the expression vector) was purified using Qiagen tip-500 columns (Qiagen Inc., Chatsworth, California USA).

Figures 2-6 identify the different human DNase I variants that were made. In the figures and throughout the specification, the description of the amino acid substitution mutation(s) present in a DNase I variant is abbreviated by a first alphabetical letter, a number, and a second alphabetical letter. The first alphabetical letter is the single letter abbreviation of amino acid residue in native (wild-type) human mature DNase I, the number indicates the position of that residue in native human mature DNase I (numbering as shown in Figure 1), and the second alphabetical letter is the single letter abbreviation of the amino acid residue at that position in the variant DNase I. For example, in the DNase I variant having a D53R mutation, the aspartic acid (D) residue at position 53 in native human mature DNase I has been replaced by an arginine (R) residue. Multiple mutations in a single variant are designated similarly, with a colon (:) separating each of the different mutations that are present in the variant. For example, the designation D53R:Y65A indicates that the variant has a D53R mutation and a Y65A mutation.

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EXAMPLE 2

Expression of Human DNase I Variants

Human embryonic kidney 293 cells (ATCC CRL 1573, American Type Culture Collection, Rockville, Maryland USA) were grown in serum containing media in 150 mm plastic Petri dishes. Log phase cells were transiently cotransfected with 22.5 µg purified variant DNA (prepared as described above) and 17 µg adenovirus DNA using the calcium phosphate precipitation method (Gorman, et al., DNA and Protein Eng. Tech. 2.3-10 (1990)). Approximately 16 hours after transfection, the cells were washed with 15 ml phosphate buffered saline and the media was changed to serum free media. Two harvests of the cell culture media were taken from each plate, the first at either 24 or 72 hours and the last at 96 hours following the serum free media change. A total of approximately 50 ml of cell culture supernatant containing the DNase I variant was obtained in this way. The pool of culture supernatant collected from each plate was concentrated 5 to 50 fold using Centriprep 10 concentrators, and the concentrates were assayed to determine various biochemical and biological activities of the DNase I variants.

Concentrate containing native human DNase I was prepared by the same procedure as described above, except that the 293 cells were transiently transfected with plasmid pRK.DNase.3

EXAMPLE 3

Biochemical and Biological Activities of Human DNase I Variants

5 I. Relative Specific Activity

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The relative specific activity of DNase I variants was assessed by comparing the activity of the variant to that of native human DNase I in two different assays. In particular, the relative specific activity of the variants is defined as the concentration of the variant (in µg/ml) determined in a methyl green activity assay (Sinicropi, et al., Anal. Biochem. 222:351-358 (1994): Kurnick, Arch. Biochem. 29:41-53 (1950)) divided by the concentration of the variant (in µg/ml) determined in a DNase I ELISA assay (described below). In both the methyl green activity assay and the DNase I ELISA assay, the standard curves were determined using Pulmozyme® human DNase I. The relative specific activity of native human DNase I and variants are shown in Figures 2A-D.

The methyl green activity assay (Sinicropi, et al., Anal. Biochem. 222:351-358 (1994); Kurnick, Arch. Biochem. 29:41-53 (1950)) utilizes methyl green dye, which intercalates approximately every 10 bases in the DNA, resulting in a green substrate. As the DNA is cleaved by the DNase I, the methyl green dye is released and oxidized to a colorless form. Thus, the loss of green color is proportional to the amount of DNase I added to the assay sample. The amount of DNase I present in the assay is then quantitated by comparison to a standard curve that is prepared by assaying known quantities of DNase I.

The DNase I ELISA assay involves coating microtiter plates with a goat anti-DNase I polyclonal antibody, adding the sample to be assayed, and detecting any resulting bound DNase I with a rabbit anti-DNase I polyclonal antibody which is conjugated to horseradish peroxidase (HRP). When HRP substrate and color development reagent are added, the color developed is proportional to the amount of DNase I present in the sample. The amount of DNase I present in the assay is then quantitated by comparison to a standard curve that is prepared by assaying known quantities of DNase I.

In both assays, multiple dilutions of the samples were assayed and those values which fell in the midrange of the standard curve were averaged and standard deviations calculated.

Also, the DNase I concentration as determined by the DNase I ELISA assay was used to standardize DNase I concentrations in other assays in which the DNase I variants were characterized (e.g., in assays of inhibition by actin, described below).

II Actin Inhibition of DNase I Hydrolytic Activity

G-actin (Kabsch, et al., Ann. Rev. Biophys. Biomol. Struct. 21 49-76 (1992)) was prepared by dialyzing overnight a 1 mg/ml solution of actin (obtained either commercially (Sigma, St. Louis, Missouri USA) or prepared by the method of Pardee, et al., Meth. Enzymol 85:164-181 (1982)) against 5 mM HEPES, pH 7.2, 0.2 mM CaCl₂, 0.5 mM ATP, 0.5 mM β-mercaptoethanol at 4°C. After centrifugation at 13,000 x g for 5 min. the amount of G-actin was quantitated by measuring the absorbance at 290 nm; a 1 mg/ml solution has an

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absorbance of 0.66 OD. The amount of G-actin preparation required to substantially (>50% inhibition) but not totally inhibit the DNA-hydrolytic activity of native human DNase I was determined in preliminary experiments under the same conditions used for each assay.

Sensitivity to actin inhibition was assessed by measuring the DNA-hydrolytic activity of the variants in the presence and absence of actin in either of two different assays, the methyl green assay previously described and a hyperchromicity assay which is based on the increase in absorbance at 260 nm upon denaturation and depolymerization of DNA (Kunitz, J. Gen. Physiol. 33:349-362 (1950); Kunitz, J. Gen. Physiol. 33:363-377 (1950)). The percent inhibition of selected variants in these assays are shown in Figures 3 and 4.

In the hyperchromicity assay, concentrated culture supernatants (prepared as described above, containing DNase I variants) were incubated either with no added or a 2- to 3-fold molar excess of actin in buffer A (25 mM HEPES, pH 7.5, 4 mM CaCl₂, 4 mM MgCl₂, 0.1% BSA) for one hour at room temperature before being added to a cuvette containing 40 µg DNA in a total assay volume of 1.0 ml. The final concentration of the DNase I variant in the assay was approximately 26 nM, as determined by DNase I ELISA assay. The rates of DNA hydrolysis by the DNase I variants in the presence and absence of actin were measured The percent activity shown in Figures 3 and 4 was calculated by determining the ratio of the DNA hydrolytic activity of the human DNase I (native or variant) in the presence of actin to its DNA-hydrolytic activity in the absence of actin and multiplying by 100.

In the methyl green assay, concentrated culture supernatants (prepared as described above, containing DNase I variants) were incubated either with no added actin or a 1000-fold molar excess of actin in buffer B (25 mM HEPES, pH 7.5, 4 mM CaCl₂, 4 mM MgCl₂, 0.1% BSA, 0.01% thimerosal, and 0.05% Tween 20) at 37°C for 16 hours. The concentration of active enzyme in each case was estimated by comparison with the standard curve of Pulmozyme®. The "percent activity" remaining of the variant refers to the 100 times the ratio of the activity in the presence of actin to the activity in the absence of actin.

As shown in Figures 3 and 4, the DNA-hydrolytic activity of native human DNase is substantially reduced in the presence of actin. By comparison, various single- and multiple-residue variants of native human DNase are relatively resistant to inhibition by actin, as indicated by their having greater DNA-hydrolytic activity in the presence of actin than native human DNase I.

III. Actin Binding ELISA

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A microtiter based assay was developed to measure the binding of native human DNase I and DNase I variants to immobilized actin. First, the wells of a MaxiSorp plate (Nunc, Inc., Naperville, Illinois, USA) were coated with 100 ul per well human GC globulin (Calbiochem, La Jolla, California USA), an actin binding protein (Goldschmidt-Clermont, et al, Biochem, J. 228:471-477 (1985), McLeod, et al., J. Biol. Chem. 264:1260-1267 (1989), Houmeida, et al., Eur. J. Biochem. 203:499-503 (1992)), at a concentration of 10 ug/ml in 25 mM HEPES, 4 mM MgCl₂, 4 mM CaCl₂, pH 7.2, at 4°C for 16-24 hours. After discarding the GC globulin, excess reactive sites were blocked by the addition of 200 ul per well buffer C (buffer C is the same as buffer B, above, with the addition of 0.5 mM adenosine triphosphate.

buffer C was used as the assay diluent in all subsequent steps unless otherwise noted) and incubating the plate on a shaker for 1-2 hours at room temperature. Each incubation step which follows was carried out at room temperature for one hour on a Mini Orbital Shaker (Bellco Biotechnology, Vineland, New Jersey USA); between each of the steps, the plate was emptied and washed 6 times with phosphate buffered saline containing 0.05% Tween 20 with a Microwash II plate washer (Skatron A/S, Norway). Next, G-actin, prepared as described above, was diluted to 50 ug/ml in buffer C and 100 ul was added to each well; the plates were incubated and washed, and 100 ul of various dilutions of Pulmozyme® and cell culture media containing either native human DNase I or variants thereof were added to the wells and the plates incubated and washed. Finally, 100 ul of a 1/25,000 dilution of an anti-human DNase I rabbit polyclonal antibodyhorseradish peroxidase conjugate (original stock concentration was 465 ug/ml) was added to each well. After incubation and washing, color development was initiated by the addition of 100 ul per well color development reagent (Sigma Fast o-phenylenediamine and urea/H2O2 tablets solubilized according to the manufacturer's recommendation) and stopped by the addition of 100 ul per well 4.5 N H₂SO₄. The absorbance at 492 nm was recorded and plotted versus the concentration of DNase I originally added to the well. Sigmoidal curves resulted for native human DNase I and those variants which bound to actin; these curves were fit to a four parameter equation by nonlinear regression analysis (Marquardt, J. Soc. Indust. Appl. Math. 11:431-441 (1963); the concentration of each DNase I (native or variant) required to give a half-maximal signal in the assay was calculated from the curves and is referred to as the EC50 value. The molecular mass of native human DNase I and the variants was assumed to be 37,000 Daltons.

The relative binding affinity of each human DNase I variant was calculated by dividing the EC₅₀ value of the variant by the EC₅₀ value of native human DNase I determined in the ELISA assay, and the results are shown in Figures 5A-D. By way of example, if the relative binding affinity of the human DNase I variant were calculated to be 5, this value would indicate that the EC₅₀ value of the variant is 5-fold greater than the EC₅₀ value of native human DNase, or in other words, that the variant has an affinity for actin that is 5-fold less than the affinity of native human DNase I for actin in this ELISA assay.

IV. Sputum Compaction Assays

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A sputum compaction assay (PCT Patent Publication No. WO 94/10567, published May 11, 1994) was used to measure the relative viscoelasticity of sputum from cystic fibrosis patients ("CF sputum") before and after incubation with native human DNase I and different DNase I variants. After mixing CF sputum with a DNase I sample and incubating for 20 min at room temperature, the semi-solid solutions were loaded into capillary tubes which then were centrifuged at 12,000 rpm for 20 minutes. Following centrifugation, the height of the pellet was measured and compared to the height of the solution plus pellet. These measurements were then used to calculate the percent compaction of the sputum, which correlates with the viscoelasticity of the sputum

The percent compaction determined upon treatment of CF sputum with native human DNase I and human DNase I actin-resistant variants is shown in Figure 6. These results indicate that the human DNase I

actin-resistant variants are more effective than native human DNase I in reducing the viscoelasticity of CF sputum, as determined by the compaction assay.

SEQUENCE LISTING

- (1) GENERAL INFORMATION:
 - (i) APPLICANT: Genentech, Inc.
 - (ii) TITLE OF INVENTION: HUMAN DNASE I VARIANTS
- 5 (iii) NUMBER OF SEQUENCES: 98
 - (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Genentech, Inc.
 - (B) STREET: 460 Point San Bruno Blvd
 - (C) CITY: South San Francisco
 - (D) STATE: California

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3.5

- (E) COUNTRY: USA
- (F) ZIP: 94080
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk
- 15 (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: WinPatin (Genentech)
 - (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER:
- 20 (B) FILING DATE:
 - (C) CLASSIFICATION:
 - (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: PCT/US95/02366
 - (B) FILING DATE: 02/24/95
- 25 (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Johnston, Sean A.
 - (B) REGISTRATION NUMBER: 35,910
 - (C) REFERENCE/DOCKET NUMBER: P0925P1PCT1
 - (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: 415/225-3562
 - (B) TELEFAX: 415/952-9881
 - (C) TELEX: 910/371-7168
 - (2) INFORMATION FOR SEQ ID NO:1:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amino Acid
 - (D) TOPOLOGY: Linear
 - (ii) MOLECULE TYPE: Amino Acid
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
- 40 Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys
 1 5 10 15

Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser

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25	Ile Pro I	Asp Se	r Ala 200		Th	Thi	r Ala	Thr 205		Thi	His	s Cys	210
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	(2) INFOR	OITAM	1 FOR	SEQ	ID	N O : 2	:						
35	(<i>F</i>	QUENCI LENG TYPE TOPG	GTH: E: Am OLOGY	260 nino (: Li	amin Acid near	io ac l	ids						

(xi)	SEQUENCE	DESCRIPTION:	SEO	TD	NO.2.	

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(2) INFORMATION FOR SEQ ID NO:3:

5	(<i>F</i>	EQUENCE A) LES (A) TY: (B) TO (C) CLECU	NGTH: PE: F POLOC	260 Amino BY L	ami Aci inea	ino a id ar	acid	S						
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3 C	Met Gl	y Asp	Phe	170		Gly	Cys	s Ser	175	Val	Arg	g Pro	Ser	Gln 180
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255

245 250

Glu Val Met Leu Lys 260

30

(2) INFORMATION FOR SEQ ID NO:4:

- 5 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 260 amino acids
 - (B) TYPE: Aminc Acid
 - (D) TOPOLOGY: Linear
 - (ii) MOLECULE TYPE: Amino Acid
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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1 5 10 15

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Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu
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Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro 50 55 60

Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn Ser 20 65 70 75

Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser 80 85 90

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95 100 105

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Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln 170 175 180

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Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala 200 205 210

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	(x :	i) Si	EQUE	NCE I	DESC	RIPT	ON:	SEQ	ID 1	10 : 5 :					
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	Ala	a Pro	Gly	/ Asp	Ala 140		Alā	a Glu	Ile	Asp 145		Let	туг	Asp	0 Val
3 5	Туг	r Lev	ı Asp	o Val	Glr 155		Lys	Trp	Gly	Leu 160		ı Asp	o Val	Met	Let 169
	Met	t Gly	Y Ası	p Phe	e Asr 170		a Gly	y Cys	s Ser	Tyr 175		Arg	g Pro	Se:	r Gli 180

	Trp	Sei	r Sei	r Ile	2 Arg	g Lei	u Trį	o Th	r Se	r Pro		r Phe	e Gl	n Tr	p Leu 195
	Ile	Pro	Asp	Se:	200	a Asp	o Thi	r Th:	r Ala	a Thi		o Thi	r Hi	s Cy	s Ala 210
5	Tyr	Asp	Arg	J Il∈	215	. Val	l Ala	a Gly	y Met	220		ı Arg	g Gl	y Ala	a Val 225
	Val	Pro	Asp	Ser	Ala 230	Let	: Pro	⊃ Ph∈	e Ası	235		n Ala	a Ala	а Ту	r Gly 240
10	Leu	Ser	Asp	Gln	Leu 245	Ala	Glr	Ala	ı Ile	250		His	ту:	r Pro	255
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-27-

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20	(:	(1	A) LI B) T	ENGTI YPE :	CHARA H: 26 Amir OGY:	50 at	mino cid		ds						
	(x	i) S	EQUE	NCE :	DESCI	RIPT	ION:	SEQ	ID	NO : 7	:				
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	Asp	Thr	Tyr	His	Tyr 65		Val	Ser	Glu	Pro 70		Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80		Phe	Val	Туг	Arg 85		Asp	Glr	val	Ser 90
35	Ala	Val	Asp	Ser	Tyr 95		Tyr	Asp	Asp	100		s Glu	ı Pro	Cys	Gly 105

	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130		Pro	Leu	Hıs	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145		Leu	Tyr	Asp	Val 150
5	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160		Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
10	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
15	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
20	Glu	Val	Met	Leu	Lys 260										
	(2)	NFO	RMAT:	ION I	FOR S	SEQ :	ID N	8:0							
25	(:	(1	EQUE: A) LE B) T: D) T(ENGTI YPE :	1: 26 Amir	0 ar 10 A	nino cid		is						
	(xi	L) SI	EQUE	VCE I	DESCR	PT	: NO	SEQ	ID 1	NO : 8	:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
3 C	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Asp	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
15	Asp	Thr	туr	His	Tyr 65	Val	Val	Ser	Glu	Prc 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90

	Ala	Val	Asp	Ser	Tyr 95	Tyr	Туr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
5	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	Hıs	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
1 C	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
15	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215		Ala	Gly	Met	Leu 220		Arg	Gly	Ala	Val 225
20	Val	Pro	Asp	Ser	Ala 230		Pro	Phe	Asn	Phe 235		Ala	Ala	Tyr	Gly 2 4 0
	Leu	Ser	Asp	Glr	Leu 245		Gln	Ala	Ile	Ser 250		His	Tyr	Pro	Val 255
	Glu	val	L Met	: Lev	1 Lys 260										
25	(2)	INF	ORMAT	иог	FOR	SEQ	ID N	10 : 9 :	:						
			SEQUI (A) I (B) I	LENG: TYPE	TH: 2 : Ami	260 a	amino Acid								
30	(:	xi)	SEQU	ENCE	DES	CRIP'	rion	: SE	O ID	NO : 9	€ :				
		u Ly 1	s Il	e Al		a Pho	e Ası	n Ile	e Gli	n Thi		e Gly	y Glu	Thi	Lys 15
	Ме	t Se	r As	n Al	a Th		u Va	l Se	r Ty	r Il		l Gli	n Ile	e Lei	Ser 30
3 5	Ar	g Ty	r As	p Il		a Le 5	u Va	l Gl	n Gl	u Va 4		g As	p Se	r Ty:	r Leu 45
	Th	r Al	a Va	l Gl		s Le C	u Le	u As	p As		u As 5	n Gl	n As	p Al.	a Pro

	Ası	o Th:	r Ty	r His	65 65	Val	. Val	. Ser	Glu	Pro 70		Gly	/ Arg	g Asi	1 Se:
	Туг	Lys	s Glu	ı Arg	Tyr 80	Leu	Phe	· Val	Tyr	Arg 85		Asp	Gln	val	. Se:
5	Ala	val	Asp) Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	: Gly
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
10	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 1 4 0	Val	Ala	Glu	Ile	As p	Ala	Leu	Tyr	Asp	Val
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
15	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
20	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Prc	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
25	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala		Ser . 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2) I	NFOF	ITAM	ON F	OR S	EQ I	D NO	:10:							
30	(i	(A	A) LE	CE C NGTH PE: 1	: 26 Amin	0 am 0 Ac	ino id	CS: acid	s						
	(xi) SE	QUEN	CE D	ESCR	IPTI	ON:	SEQ	ID N	0:10:	:				
35	Leu :	Lys	Ile .	Ala 1	Ala :	Phe 1	Asn :	Ile (Gln 7	Thr F	Phe C	Gly (Glu :	r hr :	Lys 15

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25

Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser

20

	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp .	Ser '	rp I	45
	Thr	Ala	Val	Gly	Lys 50	Гел	Leu	Asp	Asn	Leu 55	Asr.	Gln	Asp .	Ala l	Pro 60
5	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn .	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Glr.	Val	Ser 90
ιo	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110		Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	val 125		Glu	Phe	Ala	11e 130	Val	Pro	Leu	His	Ala 135
15	Ala	a Pro	o Gly	Asp	Ala 140		Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Туз	r Le	ı Asp	Va]	l Glr 155		Lys	Trp	Gly	/ Le u	Glu	Asp	Val	Met	Leu 165
20	Me	t Gl	y Ası	p Phe	e Ası		a Gly	, Cys	s Sei	Tyr 175	val	Arg	Pro	Ser	Gln 180
	Tr	p Se	r Se	r Il	e Ar		u Trj	o Thi	r Sei	r Pro	Thr	Phe	Gln	Trp	Leu 195
	11	e Pr	o As	p Se	r Al 20		p Th	r Th	r Ala	a Th i	r Pro	o Thr	His	: Cys	Ala 210
25	ту	r As	p Ar	g Il	e Va 21		1 A l	a Gl	у Ме	t Le ⁻ 22	u Lei 0	u Arg	g Gly	/ Ala	Val 225
	Va	al Pr	o As	p Se	r Al 23		u Pr	o Ph	e As	n Ph 23	e Gl: 5	n Ala	a Ala	а Туг	Gly 240
30	L€	eu Se	er As	sp Gl	ln Le 24		la Gl	n Al	a Il	e Se 25	r As	p Hi	s Ty:	r Pro	255
	G.	lu V	al Me	≥t Le		/s 60									
	(2) IN	FORM	OITA	N FO	R SE	Q ID	NO: 3	11:						

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amino Acid

35

- (D) TOPOLOGY: Linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

	-	<u>.</u>			5					10)				Lys 15
	Met	Se:	r Asr	Ala	Thr 20	Leu	Val	Ser	Тут	11e		Gln	Ile	Lei	Ser 30
5	Arg	у Ту	r Asp	Ile	Ala 35	Leu	Val	Glr	Glu	Val		Asp	Ser	Hıs	Leu 45
	Thi	: Ala	a Val	Gly	Lys 50	Leu	Leu	Ala	Asn	Leu 55		Gln	Asp	Ala	Pro 60
10	Asp	Thi	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro		Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	туг	Arg 85		Asp	Gln	Val	Ser 90
	Ala	Val	. Asp	Ser	Тут 95	Tyr	Tyr	Asp	qeA	Gly 100	Cys	Glu	Pro	Cys	Gly 105
15	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
25	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
30	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu . 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
35	Glu	Val	Met	Leu :	Lys 260										

- (2) INFORMATION FOR SEC ID NO:12:
 - (i) SEQUENCE CHARACTERISTICS.

(A) LENGTH: 260 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

	() 1	, 52	Q O DI.					_							
5	Leu 1	Lys	Ile	Ala .	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly (Glu T	hr L	ys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	туг	Ile 25	Val	Gln	Ile I	Leu S	Ser 30
10	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser I	His I	Seu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Lys	Asn	Leu 55	Asn	Gln	Asp 2	Ala I	Pro 60
	Asp	Thr	Tyr	His	Туг 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn :	Ser 75
15	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val .	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Туг	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
20	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125		Glu	Phe	Ala	Ile 130	Val	Pro	Leu	Hıs	Ala 135
	Ala	Pro	o Gly	Asp	Ala 140		Ala	Glu	ılle	Asp 145		Leu	Tyr	Asp	Val 150
25	ту	Lev	ı Asp	Val	Glr 155		ı Lys	Trp	o Gly	/ Leu 160		Asp	Val	Met	Leu 165
	Me	c Gl	y Ası	p Phe	2 Asr		a Gly	/ Cys	s Ser	Tyr 175		Arg	Pro	Ser	Gln 180
30	Tr	p Se	r Se	r Ile	e Arg		u Trp	Th:	r Sei	r Pro		Phe	Gln	Trp	Leu 195
	Il	e Pr	o As	p Se	r A la		p Th	r Th	r Ala	a Thi		o Thr	His	Cys	Ala 210
	ту	r As	p Ar	g Il	e Va 21		1 Al	a Gl	у Ме	t Lei 22		ı Arg	g Gly	Ala	Val 225
35	Va	l Pr	o As	sp Se	r Al 23		u Pr	o Ph	e As	n Ph 23	e Gl:	n Ala	a Ala	Tyr	Gly 240
	L€	eu Se	er As	p Gl	n Le 24		a Gl	n Al	a Il	e Se 25	r As	рHi	s Tyr	Pro	Val 255

Glu Val Met Leu Lys 260

5

(2) INFORMATION FOR SEQ ID NO:13:

(i SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids
(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

	(x:	i) SI	EQUE	ICE I	DESC	RIPT	ION:	SEQ	ID 1	NO:1	3:				
10	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Arg	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Prc	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
30	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	qeA	Phe	As n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
35	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225

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	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 2 4 5	Ala	Gln	Ala	lle	Ser 250	Asp	His	Tyr	Pro	Val 255
5	Glu	Val	Met	Leu	Lys 260										
	(2) 1	NFOF	I TAMS	ON F	OR S	EQ I	D N C	:14:							
10	(i	(<i>p</i>	A) LE		1: 26 Amır	o an			ls						
	(x i	i) SE	EQUE	NCE I	ESCF	RIPTI	: NO	SEQ	ID N	J O:14	: :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
15	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
20	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Tyr	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
25	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Сув	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
30	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Glγ	Leu 160	Glu	Asp	Val	Met	Leu 165
3 5	Met	Gly	Asp	Phe	As n 170		Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185		Trp	Thr	Ser	Pro 190		Phe	Gln	Trp	Leu 195

	Ile Pro Asp Se	Ala Asp Th	r Thr Ala	Thr Pro Th	r His Cys Ala 210
	Tyr Asp Arg Ile	215		220	225
5	Val Pro Asp Ser	230		235	240
	Leu Ser Asp Gln	443	n Ala Ile :	Ser Asp His 250	Tyr Pro Val 255
10	Glu Val Met Leu	260			
	(2) INFORMATION	FOR SEQ ID 1	10:15:		
15	(B) TYPE:	CHARACTERIST H: 260 amino Amino Acid DGY: Linear	CICS: acids		
	(xi) SEQUENCE I	DESCRIPTION:	SEQ ID NO	:15:	
	Leu Lys Ile Ala 1	Ala Phe Asn 5	Ile Gln T	hr Phe Gly 10	Glu Thr Lys 15
20	Met Ser Asn Ala	20		25	30
	Arg Tyr Asp Ile	33	•	10	45
	Thr Ala Val Gly	30	ī	5.5	60
25	Asp Thr Tyr His	0.5	-	' C	75
	Tyr Lys Glu Arg	80	8	5	90
30	Ala Val Asp Ser	95	10	0	105
	Asn Asp Thr Phe	Asn Arg Glu	Pro Ala Il 11	e Val Arg 1 5	Phe Phe Ser 120
		. 2 3	13	0	135
35		40	14	5	150
	Tyr Leu Asp Val G	ln Glu Lys '	Irp Gly Let 160	u Glu Asp V	al Met Leu 165

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	Met	Gly	Asp	Phe	Asn 170	Ala	Gl	у Су	's Se	er	Tyr 175	Val	Arg	Pr	o Se	r G	BC
	Trp	Ser	Ser	Ile	Arg 185	Lev	ı Tr	p Th	nr S	er	Pro 190	Thr	Phe	Gl	n Tr	ep Lo	eu 95
5	Ile	Pro	Asp	Ser	Ala 200	Ası	p Th	ir Tì	nr A	la	Thr 205	Pro	Thr	- Hi	s Cy	/s A 2	la 10
	Tyr	Asp	Arg	Ile	Val 215	Va:	l Al	a G	ly M	let	Leu 220	Leu	Arg	g Gl	.у А	la V 2	al 25
10	Val	Pro	Asp	Ser	Ala 230		u Pi	co P	he A	sn	Phe 235	Glr	ı Ala	a A.	la T	yr G	1y 240
	Leu	Ser	Asp	Gln	Leu 245		a G	ln A	la l	Ile	Ser 250	Ası) Hi	s T	yr P	ro V	/al 255
	Gli	ı Val	l Met	Leu	1 Lys 260												
15	(2)	INF	ORMA!	rion	FOR	SEÇ) ID	NO:	16:								
		(i)	SEQUI (A) : (B) :	LENG' TYPE	TH: : Am	260 ino	ami Aci	no a	CS: acid	s							
20	(xi)	SEQU	ENCE	DES	CRI	PTIC)N: :	SEQ	ID	NO:	16:					
	Le	u Ly 1	s Il	e Al	a Al	a P 5	he <i>l</i>	\s n	Ile	Gli	n Th	r Ph O	ne G	ly (3lu '	Thr	Lys 15
	Me	t S€	er As	n Al		ar L	eu 1	Val	Ser	ТУ	r Il 2	e Va 5	al G	ln	Ile	Leu	Ser 30
25	Aı	g Ty	yr As	sp Il		la I 35	.eu	Val	Gln	G1	u Va	11 A:	rg A	sp	Ser	His	Leu 4 5
	Tì	nr A	la Va	al G	ly L	ys I 50	Leu	Leu	Asp	As	n Le	eu A 55	sn G	ln	Asp	Ala	Pro 60
30	A	sp T	hr T	уг н		rg ' 65	Val	Val	Ser	Gl	u P	ro L 70	eu C	sly	Arg	Asn	ser 75
	Т	yr L	ys G	lu A	rg T	yr 80	Leu	Phe	Val	Т	yr A	rg P 85	rc l	Asp	Gln	Val	Ser 90
	A	.la V	al A	sp S	er T	`yr 95	Tyr	Tyr	Asp) A:	sp G 1	ly (Cys (Glu	Pro	Cys	: Gly 105
35	P	Asn A	Asp T	Chr F		Asn 110	Arg	Glu	Pro	А с	la I	le V	/al	Arg	Phe	Phe	ser 120
	,	Arg 1	Phe 1	Thr (Val	Arg	Glu	ı Ph	e A	la I	lle '	Val	Pro	Leu	Hls	s Ala 135

	Al	a P:	ro Gi	ly A	sp A	la v 40	/al	Ala	a Gl	u I	le	Asp 145	Ala	a Le	u T	yr i	Asp	Val 150
	ту	r Le	eu As	sp V	al G	ln (Slu	Lys	Tr	p G	ly :	Leu 160	Glι	ı As	p V	al M	1et	Leu 165
5	Ме	t Gl	y As	sp Pi	ne As	sn A 70	la	Gly	Су	s Se	er 1	Tyr 175	Val	Ar	g P:	ro S	Ser	Gln 180
	Tr	p Se	r Se	r I	le A1	ig L	eu	Trp	Th	r Se	er I	Pro 190	Thr	Ph	e Gl	n T	rp	Leu 195
10	Ile	e Pr	o As	p Se	r Al 20	a A	sp	Thr	Thi	c Al	.a 1	Thr 205	Pro	Th	r Hi	s C	ys	Ala 210
	Tyr	As	p Ar	g Il	e Va 21	1 V.	al	Ala	Gly	⁄ Me	t L 2	eu 20	Leu	Arg	g Gl	у А	la	Val 225
	Val	Pr	o As	p Se	r Al 23	a Le	eu	Pro	Phe	: As	n P 2	he 35	Gln	Ala	Al	аТ	yr	Gly 240
15	Leu	Se	r Ası	o Gl	n Le 24	u A] 5	la	Gln	Ala	Il	e S 2	er . 50	Asp	His	ту	r P		Val 255
	Glu	Va:	l Met	Le	u Ly:													
	(2)	INFO	RMAT	TION	FOR	SEÇ) I	D N O	:17	:								
20	(.	(EQUE A) L B) T D) T	ENGT YPE :	TH: 2 : Ami	260 .no	am: Ac:	ino id	CS: acio	ds								
	(x:	i) s	EQUE	NCE	DESC	RIP	TIC	. : и с	SEQ	ID	NO:	17:						
25			Ile			Ph					Th			Gly	Glu	Th	r I	ys 15
	Met	Ser	Asn	Ala	Thr 20	Lei	u V	al s	Ser	Tyr	11	e V 5	al (31n	Ile	Le	u S	er 30
30	Arg	Tyr	Asp	Ile	Ala 35	Let	ı V	al (Sln	Glu	Va 4	A C	rg A	Asp	Ser	Hi		eu 45
	Thr	Ala	Val	Gly	Lys 50	Let	ı L	eu A	sp.	Asn	Le ²	u A: 5	sn G	In	Asp	Ala		ro 60
	Asp	Thr	Tyr	His	Trp 65	Val	V	al S	er	Glu	Pro	D L e	eu G	ly	Arg	Asr		er 75
35	Tyr	Lys	Glu	Arg	Tyr 80	Leu	ı Pl	he V	al 1	Tyr	Arg 85		CO A	sp	Gln	Val		er 90
	Ala v	Val	Asp	Ser	Tyr 95	Tyr	Т	yr A	sp A	qaA	Gl _y		s G	lu :	Pro	Cys		ly 15

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	Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser	
	Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 125 130 135	
5	Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val	
	Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu 155 160 165	
10	Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln 170 175 180)
	Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 185 190 195	1
	Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala 200 205 210	a D
15	Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Val 215 220 229	1 5
	Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gl 230 235 24	У 0
20	Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Va 245 250 25	1 5
	Glu Val Met Leu Lys 260	
	(2) INFORMATION FOR SEQ ID NO:18:	
25	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 260 amino acids(B) TYPE: Amino Acid(D) TOPOLOGY: Linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:	
30	Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr L	ys 15
	Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu S 20 25	er 30
	Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His L	eu 45
35	Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala P	00 60
	Asp Thr Tyr His Tyr Val Ala Ser Glu Pro Leu Gly Arg Asn S	3 e :

	Tyr	Lys	Glu	Arg	Tyr 8C	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gl ₃
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	Hıs	Ala 135
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Let 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Glr 180
15	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asa	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	туr	Pro	Val 255
25	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMATI	ION I	FOR S	SEQ :	ID NO):19	:						
3 0	(:	() ()		ENGTI (PE :	4: 26 Amir	o ar			is						
	(x i	i) S	EQUEN	ICE I	DESC	RIPT	ON:	SEQ	ID 1	NO:19) :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
3 5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45

	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Glu	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	qeA	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	туг	Gly 240
	Leu	Ser	Asp	Gln	Leu 245		Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
30	Glu	ı Val	. Met	Leu	Lys 260										
	(2)	INFO	RMAT	CION	FOR	SEQ	ID N	10:20	:						
	,		(A)	ENCE LENGT TYPE :	H: 2	60 a	mino								

- 35 (D) TOPOLOGY: Linear
 - (x1) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys
1 5 10 15

	Met	: Sei	r Ası	n Ala	Thr 20	Leu	Val	. Ser	Tyr	Ile 25		Gln	lle	. Lei	3 Sei
	Arg	туг	c Asp) Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp) Ser	Нав	Let
5	Thr	Ala	a Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55		Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Lys	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
10	Tyr	Lys	Glu	Arg	Туr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	As n 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	туг	Asp	Val 150
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe		Phe 235	Gln	Ala	Ala	Tyr	Gly 2 4 0
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala		Ser . 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

35 (2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amino Acid
 - (D) TOPOLOGY: Linear

xi) SEQ	UENCE	DESCRIPTION:	SEQ	ID	NO:21:	
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	(XI	, 35	QUEN	CE D			O	022		· • •	•				
	Leu 1	Lys	Ile	Ala .	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Туг	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Lys	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Ąsp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140		Ala	Glu	Ile	Asp 145		Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	val	Gln 155		Lys	Trp	Gly	Leu 160		Asp	Val	Met	Leu 165
25	Met	Gly	/ Asp	> Phe	170		Gly	Cys	Ser	Tyr 175		Arg	Pro	Ser	Gln 180
	Trp	Ser	s Ser	r Ile	Arg		ı Trp	Thr	Ser	Pro		Phe	Gln	Trp	Leu 195
	Ile	e Pro	o Asp	Ser	Ala 200		o Thr	Thr	- Ala	Thr) Thr	His	cys	Ala 210
30	Ту	c Asj	p Ar	g Ile	≥ Va:		l Ala	a Gly	/ Met	Leu 220		ı Arg	g Gly	/ Ala	Val 225
	Va:	l Pr	o As	p Sei	r Al. 23		u Pro	o Phe	e Ası	n Phe 235		n Ala	a Ala	а Туг	Gly 240
35	Le	u Se	r As	p Gli	n Le		a Gli	n Ala	a Il	e Sei 250		p Hi:	s Ty	r Pro	Val 255
33	Gl	u Va	l Me	t Le		s									
	(2)	INF	'ORMA	TION			ID	NO : 2	2:						

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

5	(x	i) S	EQUE	NCE	DESC	RIPT	'ION :	SEÇ	ID	N O : 2	2:				
	Leu 1		Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10		Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25		Gln	Ile	Leu	Ser 30
10	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
15	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Arg	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
			Asp		95					100					105
20			Thr		110					115					120
			Thr		125					130					135
25			Gly		140					145					150
			Asp		155					160					165
			Asp		170					175					180
30			Ser		185					190					195
			Asp		200					205					210
35			Arg		215					220					225
			Asp		230					235					240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	Hıs	Tyr	Pro	Val 255

Glu Val Met Leu Lys 260

5

(2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Aminc Acid
 - (D) TOPOLOGY: Linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:23:

10	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Ala	Leu 45
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Arg	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Туг 95	Tyr	Туr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
30	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
35	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220		Arg	Gly	Ala	Val 225

Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly 230 Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val 245 Clu Val Met Leu Lys

(2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
- 10 (B) TYPE: Amino Acid
 - (D) TOPOLOGY: Linear

155

170

35

	(×	i) S	EQUE:	NCE	DESC	RIPT	ION:	SEQ	ID	NO : 2	4:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
15	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
20	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Arg	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Ala 65	Val	Val	Ser	Glu	Pro	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
25	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
30	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp		Leu	Glu	Asp	Val	Met	Leu

Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln

Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Glr. Trp Leu

175

	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
5	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
10	Glu	Val	Met	Leu	Lys 260										
	(2)	NFO	RMAT	ION I	FOR S	EQ I	D NC	: 25	:						
15	()	(:	A) Li B) T	ENGTI YPE :	CHARA H: 26 Amir DGY:	0 an	mino cid		is						
	(x:	i) s	EQUE	NCE I	DESCR	RIPTI	: NO	SEQ	ID 1	10 : 2 9	š :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
20	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Arg	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
25	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Arg	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
3 C	Ala	Val	. Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Сув	Glu	Pro	Cys	Gly 105
	Asn	. Asp	o Thr	Phe	110	Arg	Glu	Pro	Ala	Ile 115		. Arg	g Phe	Phe	Ser 120
	Arg	Phe	e Thi	Glu	125		Glu	Phe	Ala	11e		Pro	Let	ı His	135
35	Ala	Pro	o Gly	/ Asp	140		Ala	Glu	ılle	145		a Lei	1 Туі	. Asp) Val 150
	Туг	Lei	u Ası	o Val	l Gln 155		ı Lys	Tr	Gly	/ Let		ı Ası	o Vai	l Met	Leu 165

	Met Gly A	-				175			180
	Trp Ser S	•	0.5			190			195
5	Ile Pro A	sp Ser A 2	la Asp 00	Thr	Thr Al	la Thr I 205	Pro Thr	His Cys	Ala 210
	Tyr Asp Ai	g Ile V 2	al Val 15	Ala	Gly Me	et Leu I 220	Leu Arg	Gly Ala	. Val 225
10	Val Pro As	Sp Ser A	la Leu 30	Pro	Phe As	n Phe G 235	In Ala	Ala Tyr	Gly 240
	Leu Ser As	p Gln Le	eu Ala 15	Gln .	Ala Il	e Ser A 250	sp His	Tyr Pro	Val 255
	Glu Val Me	t Leu Ly 26							
15	(2) INFORMA	TION FOR	SEQ :	ID NO:	: 26 :				
	(A) (B) '	ENCE CHA LENGTH: IYPE: Am IOPOLOGY	260 am ino Ac	mino a	CS: Icids				
20	(xi) SEQU	ENCE DES	CRIPTI	ON: S	EQ ID	NO:26:			
	Leu Lys Ile 1	e Ala Al	a Phe	Asn I	le Glr	Thr Ph	ne Gly (Slu Thr	Lys 15
	Met Ser Asr	Ala Th	r Leu	Val S	er Tyr	Ile Va 25	l Gln I	le Leu	Ser 30
25	Arg Tyr Asp	lle Ala	a Leu	Val G	ln Glu	Val Ar 40	g Asp S	er Ala	Leu 45
	Thr Ala Val	Gly Lys	Leu 1	Leu A	rg Asn	Leu As: 55	n Gln A	sp Ala	Pro 60
30	Asp Thr Tyr	His Ala	Val v	Val Se	er Glu	Pro Le	u Gly A	rg Asn S	Ser 75
	Tyr Lys Glu	Arg Tyr	Leu I	Phe Va	al Tyr	Arg Pro	Asp G	ln Val S	Ser 90
	Ala Val Asp	Ser Tyr 95	Tyr T	yr As	p Asp	Gly Cys	s Glu Pr		31y .05
35	Asn Asp Thr	Phe Asn 110	Arg G	lu Pr	o Ala	Ile Val	. Arg Ph		er 20
	Arg Phe Thr	Glu Val 125	Arg G	lu Ph	e Ala	Ile Val 130	Pro Le		la 35

	Ala Pr	o Gl	y Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp '	Val 150
	Tyr Le	eu As	sp Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
5	Met Gl	.y As	sp Phe	170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp Se	er Se	er Ile	Arg	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile P	ro A	sp Sei	r Ala 200		Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr A	sp A	rg Il	e Val 215		Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val P	ro A	sp Se	r Ala 230		Pro	Phe	Asn	Phe 235		Ala	Ala	Tyr	Gly 240
15	Leu S	er A	sp Gl	n Let 245		Glr	Ala	Ile	ser 250		His	Tyr	Pro	Val 255
	Glu V	al M	let Le	u Ly: 26										
	(2) IN	IFORM	MOITAL	FOR	SEQ	ID 1	10:27	7:						
20	(i)	(A)	QUENCE) LENC) TYPE) TOPC	STH: E: Am	260 a	amino Acid	rics b ac:	: ids						
	(xi)) SE	QUENCI	E DES	CRIP	noit	: SE	Q ID	NO:	27:				
25	Leu l	Lys	Ile A	la Al	a Ph 5	e As	n Il	e Gl	n Th		e Gly	y Glu	1 Thr	Lys 15
	Met	Ser	Asn A		r Le	u Va	l Se	r Ty	r Il 2	e Vai	l Gl	n Ile	e Leu	Ser 30
30	Arg	Tyr	Asp I		a Le	u Va	.1 G1	n Gl		1 Ar	g As	p Se	r Alá	Leu 45
	Thr	Ala	Val G		ys Le 50	eu Le	eu As	p As		u As	n Gl	n As	p Ala	a Pro 60
	Asp	Thr	Tyr H		la Va 65	al Vá	al Se	er Ai		0 Le	u Gl	y Ar	g As:	n Ser 75
35	Tyr	Lys	Glu A		yr Le 80	eu Pl	ne Va	al Ty		rg Pr 35	o As	p Gl	n Va	1 Ser 90
	Ala	Val	Asp S	Ser T	yr T 95	yr T	yr A	sp A	sp G:	ly Cy no	s Gl	u Pr	о Су	s Gly 105

	Asr	a Asj	p Thi	Phe	As n	Arg	Glu	Pro	Ala	a Ile 115		Arg	Phe	Phe	ser 120
	Arg	g Phe	e Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130		. Pro	Leu	His	Ala 135
5	Ala	Pro	o Gly	As p	Ala 140	Val	Ala	Glu	Ile	145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Let	ı Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met	Gly	/ Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
15	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
20	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT:	ION F	OR S	EQ I	D NC	:28	:						
25	(:	()	A) Li B) T	NCE C ENGTH (PE: OPOLO	: 26 Amin	0 am	ino id		is						
	(xi	i) s	EQUE	ICE D	ESCR	IPTI	ON:	SEQ	ID 1	1 0 : 28	:				
30	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Al a 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Cys	Leu 45
35	Thr	Ala	Val	Gly :	Lys : 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln .	Asp .	Ala	Pro 60
	Asp	Thr	Tyr	His '	Tyr '	Val	Val	Ser	Glu	Pro :	Leu	Gly .	Arg 1	Asn	Ser 75

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	Tyr	Lys	Glu	Arg	Туг 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	: Gly	/ Asp	Phe	Asn 170		Gly	Cys	Ser	Tyr 175		Arg	Pro	Ser	Gln 180
15	Tr	ș Sei	r Ser	Ile	Arg		Trp	Thr	Ser	Pro		Phe	Gln	Trp	Leu 195
	Ile	e Pro	o Asp	ser	Ala 200		Thr	Thr	Ala	Thr 205		Thr	His	Cys	Ala 210
20	ту	r As	p Arg	g Ile	215		l Ala	a Gly	/ Met	Let 220		Arg	g Gly	Ala	Val 225
	۷a	l Pr	o Asi	p Sei	r Ala 230		u Pro	o Phe	e Ası	n Phe 235		n Ala	a Ala	Tyr	Gly 240
	Le	u Se	r As	p Gli	n Le		a Gl	n Al	a Ile	e Sei 25		His	з Туг	Pro	Val 255
25	G1	u Va	ıl Me	t Le	u Ly 26										
	(2)	INF	ORMA	TION	FOR	SEQ	ID	NO : 2	9:						
30		(i)	(B)	LENG TYPE	: ΗΤ: : Απ	260 ino	ERIS amin Acid near	.o ac	: :ids						
		(xi)	SEQU	JENCE	DES	CRIE	OITS	I: SE	O IE) NO:	29:				
	L	eu L	ys Il	le Al	la Al	la Ph 5	ne As	sn Il	e Gl		r Ph .0	e Gl	y Gl	u Th	r Lys 15
35	М	et S	er As	sn Al		nr Le 20	eu Va	al Se	er Ty	yr Il	e Va	ll Gl	n Il	e Le	u Ser 30
	A	rg T	yr A	sp I		la L	eu V	al G	ln G	lu Va	al Ar 10	g As	sp Se	er Gl	n Leu 45

55

Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro

	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro	Leu	Gly	Arg	Asn	Ser 75
5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp	Ala	Leu	Tyr	Asp	Va l
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 2 4 0
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
30	Glu	Val	Met	Leu	Lys 260										
	(2) I	NFOR	ITAM	ON F	OR S	EQ I	D NC	30:							
	(i		L) LE	CE C NGTH	: 26	0 am	ino		ls						
35				POLO											

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys
1 5 10 15

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	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Cys 45
5	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
10	Туr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95		Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	110	Arg	g Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	g Phe	e Thr	Glu	1 Val		g Glu	ı Phe	e Ala	130	val	Pro	Leu	His	Ala 135
	Ala	a Pr	o Gl	/ Asi	Ala 140		l Al	a Gl	u Ile	e Asp	Ala	Leu	туг	Asp	Val 150
20	ту	r Le	u Ası	p Va i	l Gl: 15		u Ly	s Tr	p Gl	y Let 16	ı Glu	ı Asp	o Val	l Met	165
	Me	t Gl	y As	p Ph	e As 17		a Gl	у Су	s Se	r Ty	r Val	l Ar	g Pro	o Sei	Gln 180
	Tr	p Se	er Se	r Il	e Ar 18		eu Tr	p Th	ır Se	r Pr 19	0 Th:	r Ph	e Gl	n Trj	p Leu 195
25	Il	e Pi	ro As	p Se	r Al		sp Th	ir Th	nr Al	a Th	r Pr	o Th	r Hi	s Cy	s Ala 210
	T	yr A	sp Ar	g []		al Va 15	al A	la G	ly M e	et Le 22	u Le	u Ar	g Gl	y Al	a Val 225
30	V	al P	ro As	sp Se		la L 30	eu P	ro P	he A	sn Ph 21	ne Gl 35	.n Al	a Al	а Ту	r Gly 240
	L	eu S	er A	sp G		eu A 45	la G	ln A	la I	le Se	er As	вр Н:	is Ty	/r Pr	co Val 255
	G	lu V	al M	et L		ys 60									
					==		- TF	NO.	. 21.						

- 35 (2) INFORMATION FOR SEQ ID NO:31:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amino Acid
 (D) TOPOLOGY: Linear

(xi)	SEQUENCE	DESCRIPTION:	SEQ	ID	NO:31:
------	----------	--------------	-----	----	--------

								_							
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Lys 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	His	Туг 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
25	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
30	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
35	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 260 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear
- 5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

5	(xi)	SEQUENCE	DESCRI	PTION:	SEQ	ID 1	NO : 32	2 :				
	Leu Ly	s Ile Al	a Ala P 5	he Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met Se	r Asn Ala	Thr L	eu Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
10	Arg Ty	r Asp Ile	Ala L 35	eu Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Arg 45
	Thr Ala	a Val Gl	Lys L 50	eu Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
15	Asp Th	r Tyr Hi	5 Tyr V 65	al Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr Ly	s Glu Arg	g Tyr L 80	eu Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala Va	l Asp Se	Tyr T 95	yr Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
20	Asn As	o Thr Pho	Asn A	irg Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg Ph	e Thr Gli	1 Val A 125	irg Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
25		o Gly As _l	140				145					150
		u Asp Val	155				160					165
		y Asp Pho	170				175					180
30		r Ser Ile	185				190					195
	Ile Pro	o Asp Se	200	sp Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
35	Tyr As	P Arg Ile	215	'al Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val Pro	o Asp Se	230	eu Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu Se	r Asp Gli	1 Leu A 245	la Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255

Glu Val Met Leu Lys 260

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 260 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:33:

			_					220	2 10	140:)) ;				
10	Let	ı Ly:	s Il	e Ala	a Ala	Phe	Asn	Ile	e Glr	Thr 10		e Gly	y Glu	ı Thr	Lys 15
	Met	Se:	r Ası	n Ala	Thr 20	Leu	Val	Ser	Туг	: Ile 25	va]	Glr	ı Ile	Leu	Ser 30
	Arç	ј Туз	r Ası	p Ile	Ala 35	Leu	Val	Gln	Glu	Val		Asp	Ser	His	Leu 45
15	Thr	Ala	a Cys	s Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55		Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
30	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Glγ	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
35	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val .	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225

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	Val P	ro	Asp	Ser	Ala 230		u P	ro l	Phe	As	n P 2	he G 35	Sln A	Ala	Al.	a T	rr (±1.Y 2.4.C)
	Leu S	er	Asp	Glr	Let 245	ı Al	a G	ln A	Ala	11	le S	er 2 50	Asp 1	His	ту	r P	ro '	Val 255	5
5	Glu V	al	Met	Let	Ly:														
	(2) IN	FOI	RMAT	101	FOR	SE) II) NO	: 34	:									
10	(i)	(; (;	A) I B) T	ENG YPE	CHA TH: : Am LOGY	260 ino	am: Ac:	ino id	CS: ac:	: ids									
					DES														
	Leu l	Lys	Ile	e Al	a Al	.a P 5	he	Asn	Il	e G	Iln	Thr 10	Phe	Gly	/ G	lu '	Thr	L)	/s .5
15	Met	Ser	As:	n Al		nr L 20	eu	Val	Se	r T	Гуr	Ile 25	Val	Gli	n I	le	Leu	Se	er 30
	Arg	Туз	c As	р І:		la I 35	Leu	Val	Gl	n (Glu	Val 40	Arg	As	p S	er	His	Le	eu 45
20	Thr	Ala	a Ly	s G	ly L	ys 1 50	Leu	Leu	ı As	sp.	Asn	Leu 55	Asn	Gl	n A	Asp	Ala	P	ro 60
	Asp	Th	r Ty	r H	is T	yr ` 65	Val	Va]	S	er	Glu	Pro	Leu	Gl	у 1	Arg	Asr	ı S	er 75
	Tyr	Lу	s G	lu A	rg T	yr 80	Leu	Phe	e V	al	Tyr	Arg 85	Pro	AS	sp (Gln	Va:	1 S	er 90
25	Ala	Va	ıl A	sp S	Ser 7	Tyr 95	туг	ту	r A	.sp	Asp	Gly	/ Cy:	s Gl	lu	Pro	Су	s C	31y 105
	Asn	As	эр Т	hr I	Phe 2	Asn 110	Arg	Gl	u P	ro	Ala	110	e Va 5	1 A:	rg	Phe	Ph	e 9	Ser 120
30	Arg	[P]	he I	hr (Glu	Val 125	Arg	g Gl	u I	he	Ala	11 13	e Va O	1 P	ro	Leu	Hı	S	Ala 135
	Alā	a P	ro C	Sly	Asp	Ala 140	Va:	l Al	.a (Glu	Ile	e As	p Al 5	a L	eu	Туг	: As	p	Val 150
	Ту	r L	eu i	Asp	Val	Gln 155		u Ly	/s	Trp	Gl	y Le 16	iu Gi 10	Lu A	sp	Va:	L Me	et	Leu 165
3 5	. Me	t G	Sly :	Asp	Phe	Asn 170	Al	a G	ly	Сув	s Se	r T)	/r Va 75	al A	٩rg	Pr	o S:	er	Gln 180
	Tr	p S	Ser	Ser	Ile	Arc	g Le	u T	rp	Thi	r Se	er Pi	ro T 90	hr 1	Phe	Gl	пТ	rp	Let 195

	Ile	e Pr	o Ası	p Se	r Al.	a As	p Th	r Th	r Al	a Th 20	r Pro	Th:	r Hi	s Cy:	s Ala 210
	Туз	r As	p Arg	g Il	e Va:	l Va.	l Ala	a Gl	у Ме	t Le		ı Arg	g Gl	y Ala	a Val 225
5	Val	Pro	o Asp	Se:	r Ala 230	a Lei	u Pro	> Phe	e As:	n Phe 23!		n Ala	a Ala	a Tyr	Gly 240
	Leu	ı Se	r Asp	Gli	1 Let 245	ı Ala	a Glr	a Ala	a Ilo	e Sei 250		His	тул	r Pro	Val 255
10	Glu	va]	l Met	Let	1 Lys 260										
	(2)	INFO	ORMAT	NOI	FOR	SEQ	ID N	10:35	5 :						
15	((ENGT YPE :	TH: 2 Ami	60 a	mino cid								
	(x	i) S	EQUE	NCE	DESC	RIPT	'ION :	SEC	ID.	NO:3	5 :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
20	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Cys	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
25	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
30	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
35	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165

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	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	/ Су	⁄s S	er	Tyr 175	Val	Arg	Pro	Se	18	30
	Trp	Ser	Ser	Ile	Arg 185	Leu	Tr	o Tì	nr S	er	Pro 190	Thr	Phe	Gln	Tr	p Le	eu 95
5	Ile	Pro	Asp	Ser	Ala 200	Asp	Thi	r Tì	nr A	la.	Thr 205	Pro	Thr	His	Су	s Al 21	la 10
	Tyr	Asp	Arg	Ile	Val 215		Ala	a G	ly N	let.	Leu 220	Leu	Arg	Gly	Al	a V	al 25
10	Val	Pro	Asp	Ser	Ala 230		ı Pr	0 P	he <i>l</i>	Asn	Phe 235	Gln	Ala	Ala	ту	r G 2	1 y 4 C
	Leu	Ser	Asp	Glm	Leu 245		a Gl	n A	la	Ile	Ser 250	Asp	His	туг	Pr	o V 2	al 55
	Glu	Val	Met	Lev	Lys 260												
15	(2)	INFO	RMAT	CION	FOR	SEQ	ID	NO:	36:								
	((LENG' IYPE		260 ino	amin Acio	no a d		ls							
20	(x	(i) S	SEQUI	ENCE	DES	CRIP	TIO	N : :	SEQ	ID	NO : 3	36:					
		ı Ly: l	s Il	e Al	a Al	a Ph 5	ie A	sn i	Ile	Glr	Th:		e Gl	y Gl	u T	hr 1	Lys 15
	Met	t Se	r As	n Al		r Le	eu V	al	Ser	Ту	r Il 2	e Va 5	1 G1	n Il	e L	eu	Ser 30
25	Arg	д Ту	r As	p Il		a Le	eu V	al	Gln	Gl ⁻	u Va 4	l Ar	g As	sp Se	er F	lis	Leu 45
	Th	r Al	a Va	1 11		/s L 0	eu L	eu	qaA	As		u As	n G	ln As	sp A	Ala	Pro 60
30	As	p Th	ır Ty	r H		yr V 65	al V	/al	Ser	Gl	u Pr	0 Le	eu G	lγ A	rg)	Asn	Ser 75
	ТУ	r Ly	/s G	lu A		yr L 80	eu l	Phe	Val	Т	r Ai	rg Pi	ro A	sp G	ln '	Val	Ser 90
	Αl	La V	al A	sp S	er T	yr T 95	yr '	Tyr	Asp	As	sp G!	ly C 00	ys G	lu P	ro	Cys	Gly 105
35	As	sn A	sp T	hr P		sr. A	rg	Glu	Pro) A	la I 1	le V 15	al A	irg P	he	Phe	Ser 120
	A:	rg P	he T	hr G		al <i>F</i>	Arg	Glu	Phe	e A	la I 1	le V 30	al E	ro L	Leu	His	Ala 135

	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
5	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Prc	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT	ION I	FOR S	SEQ :	ID NO	0:37	:						
20	(:	()	EQUENA) LI B) TY	ENGTI YPE :	H: 26 Amir	50 ar	mino cid		ds						
	(x :	i) S1	EQUE	NCE I	DESCI	RIPT	ION:	SEQ	ID 1	NO : 3	7:				
25	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
30	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Hıs	Leu 45
	Thr	Ala	Val	Lys	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Glr.	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
35	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105

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	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120	0
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	13	a 5
5	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Туг	Asp	Va 15	0
	Tyr	Leu	Asp	Val	Gln 155		ГÀа	Trp	Gly	Leu 160	Glu	Asp	Val	L Met	16	u 5
10	Met	Gly	Asp	Phe	170		Gly	Cys	: Ser	Tyr 175	Val	. Arg	y Pro	o Se	r Gl	.n 80
	Trp	Ser	Ser	Ile	2 Arg		Trp	Thr	Ser	190	Th:	Phe	e Gl	n Tr	p Le	eu 95
	Ile	e Pro	o Asp	Se 1	c Ala 200		Th:	r Thi	r Ala	a Thi	r Pro	o Th	r Hi	s Cy	s A	la 10
15	ту	r Asj	p Arg	g Il	e Va:		l Ala	a Gl	y Me	t Le	u Le O	u Ar	g Gl	y Al	a V. 2	al 25
	Va	l Pr	o As	p Se	r Al 23		u Pr	o Ph	e As	n Ph 23	e Gl 5	n Al	a Al	.а Ту	/r G 2	1 y 4 0
20	Le	u Se	r As	p Gl	n Le 24		a Gl	n Al	a Il	e Se 25	r As	p Hi	s Ty	yr Pi	ro V 2	'al !55
	Gl	.u Va	al Me	t Le	u Ly 26											
	(2)	INI	FORM	TION	1 FOF	R SEC) ID	NO:3	3 B :							
25		(i)	(A) (B)	JENCI LENG TYPI TOPG	GTH: E: A	260 mino	ami Aci	no a d	S: cids							
		(xi)	SEQ	UENC	E DE	SCRI	PTIO	N: S	EQ I	D NO	:38:					
30	L	eu L	ys I	le A	la A	la P 5	he A	sn I	le G	ln T	hr F	he G	ly (3lu 7	Chr	Lys 15
	M	iet S	Ger A	sn A	la T	hr L 20	eu V	al S	er T	yr I	le \ 25	al C	iln :	Ile :	Leu	Ser 30
	F	Arg T	Γyr A	Asp 1	le A	Ala I 35	∟eu \	/al (Sln C	Glu V	/al / 40	Arg A	Asp	Ser	His	Le u 45
35	7	Thr I	Ala '	Jal 1	Arg 1	Lys I 50	Leu 1	Leu i	Asp A	Asn l	Leu . 55	Asn (Gln	Asp	Ala	Pro 60
		Asp '	Thr '	Tyr 1	Hıs '	Tyr ' 65	Val '	Val	Ser (Glu	Pro 70	Leu	Gly	Arg	Asr.	Ser 75

Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser 80 85 90

	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
25	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT:	ION I	FOR :	SEQ :	ID N	D: 3 9	:						
30	(.	()	EQUEI A) LI B) T D) T	ENGTI YPE :	H: 20 Amin	60 at	mino cid		ds						
	(x	i) S	EQUE	NCE 1	DESC	RIPT	ION:	SEÇ	ID I	10:3	9 :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
35	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45

	Thr	Ala	Val	Tyr	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
L 0	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	As n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185		Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200		Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215		Ala	Gly	Met	Leu 220		Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230		Pro	Phe	. Asn	Phe 235		Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245		Gln	Ala	Ile	Ser 250		His	Tyr	Pro	Val 255
30	Glu	ı Val	. Met	Leu	Lys 260										
	(2)	INF	ORMAT	CION	FOR	SEQ	ID 1	10 : 40):						
			(A) I	LENGT	TH: 2	260 a	ERIST								
35			(B) ז (ח) ז												

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys 1 5 10 15

	Ме	t Se	r Ası	n Ala	Thr 20	Leu	Val	. Ser	Ту	r Ile 25	e Val	l Glr	ı Il ϵ	. Lei	Ser 30
	Arg	д Ту	r Asp	⊃ Ile	Ala 35	Leu	Val	Gln	Gli	1 Val		g Asp	Ser	His	Leu 45
5	Thi	r Ala	a Va]	l Gly	Lys 50	Leu	Cys	Asp	Ası	Leu 55		Glr	: Asp	Ala	Pro 60
	Asp	o Thi	г Туг	His	Tyr 65	Val	Val	Ser	Glu	70		Gly	' Arg	Asn	Ser 75
10	Туг	Lys	s Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85		Asp	Gln	Val	Ser 90
	Ala	va]	l Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val .	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala		Gly 240
	Leu	Ser	Asp	Gln	Leu . 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr		Val 255
	Glu	Val	Met	Leu	Lys 260										

35 (2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amino Acid
 - (D) TOPOLOGY: Linear

WU	70/202	, ,													
	(xi) SE	QUEN	CE D	ESCR:	IPTI	ON:	SEQ	ID N	10 : 4 1	:				
	Leu 1	Lys	Ile	Ala	Ala 1	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly (Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr :	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Lys	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Туг	Lys	Glu	Arg	туr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	. Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e		Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	145		Leu	Tyr	Asp	Val 150
	Tyr	Let	ı Asp	val	Gln 155	Glu	Lys	Trp	Gly	/ Let		Asp	Val	Met	Leu 165
25	Met	Gl	y Asp	o Phe	Asn 170		Gly	Cys	s Sei	r Ty:		Arg	Pro	Ser	Gln 180
	Trp	Se	r Sei	r Ile	e Arg		ı Trp	Th	r Se	r Pro		Phe	e Glr	ı Tr	195
	Ile	e Pr	o Asj	p Se:	r Ala 200		7hı	Th	r Al	a Th: 20		Thi	Hi	s Су:	s Ala 210
30	Ту	r As	p Ar	g Il	e Val		l Ala	a Gl	у Ме	t Le 22		ı Arg	g Gl	y Al	a Val 225
	Va	l Pr	o As	p Se	r Ala 230		u Pr	o Ph	e As	n Ph 23		n Ala	a Al	а Ту	r Gly 240
	Le	u Se	r As	p Gl	n Lei	ı Al	a Gl	n Al	a Il	e Se	r As	p Hi	s Ту	r Pr	o Val

Glu Val Met Leu Lys 260

3.5

(2) INFORMATION FOR SEQ ID NO:42:

250 255

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

(B) TYPE: Amino Acid(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42: Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu 10 Thr Ala Val Gly Lys Leu Met Asp Asn Leu Asn Gln Asp Ala Pro Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn Ser 15 Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly 100 20 Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser 115 Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 25 140 Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 30 185 190 Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala 200 205 Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Val 35 215 Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly 230 235 Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val 245

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Glu Val Met Leu Lys 260

5

(2) INFORMATION FOR SEQ ID NO:43:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amino Acid
 - (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

	(X)	L) S	ΕQ	OENC	E D	ESCR	1611	.ON:	SEQ	10 1	•0. •3	•				
10	Leu 1	Lys	I	le A	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly ·	Glu '	Thr	Lys 15
	Met	ser	A	sn i	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Туг	. A	sp	lle	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
15	Thr	Ala	a V	/al	Gly	Lys 50	Leu	Leu	Cys	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Th:	r T	ryr	His	Туг 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Туг	Ly	s (Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	a Va	1 2	Asp	Ser	Tyr 95		Tyr	Asp	Asp	100	Cys	Glu	Pro	Cys	Gly 105
	Ası	n As	p	Thr	Phe	110		g Glu	Pro	Ala	a Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Ar	g Ph	ıe	Thr	Glu	125		g Glu	ı Phe	e Ala	a Ile 130	val	Pro	Leu	Hls	Ala 135
						140)				14	5				150
30						15	5				16	0				165
						17	0				17	5				180
	Tı	rp S	er	Sei	: Il	e Ar 18		u Tr	p Th	r Se	r Pr 19	o Thi	r Phe	e Glr	ı Trj	195
35						20	0				20	15				s Ala 210
	T	yr P	sp	Ar	g Il	e Va 21		al Al	a G	Ly Me	et Le 22	eu Le 20	u Ar	g Gl	y Al	a Val 225

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Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val Glu Val Met Leu Lys (2) INFORMATION FOR SEQ ID NO:44: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 260 amino acids (B) TYPE: Amino Acid 10 (D) TOPOLOGY: Linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:44: Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu Thr Ala Val Gly Lys Leu Leu Leu Asn Leu Asn Gln Asp Ala Pro 20 Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn Ser Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly 25 Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 30 Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 145 Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln 35 175 Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 190

Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Val Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly 235 Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val 250 Glu Val Met Leu Lys 10 (2) INFORMATION FOR SEQ ID NO:45: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 260 amino acids (B) TYPE: Amino Acid 15 (D) TOPOLOGY: Linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45: Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser 20 Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu Thr Ala Val Gly Lys Leu Leu Met Asn Leu Asn Gln Asp Ala Pro Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn Ser 25 65 Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly 30 Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 130 35 Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 140 Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu 16C

- 70-

	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
10	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	туr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
15	(2)	INFO	RMAT:	ION I	FOR S	SEQ :	ID NO	0:46	:						
	(() (1	EQUENA) LE B) TY D) TO	engti (PE :	H: 26 Amir	60 ar	nino cid		ds						
20	(x	i) Si	EQUE	NCE I	DESCR	RIPT	: MO	SEQ	ID I	10 : 4	5:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
25	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	naA	Leu 55	Cys	Gln	Asp	Ala	Pro 60
30	Asp	m la	_		m	11-1		_				~ `	_	7	Car
		Inr	Tyr	His	65	vai	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	ASII	75
			Glu		65					70					
	Tyr	Lys		Arg	65 Tyr 80	Leu	Phe	Val	туr	70 Arg 85	Pro	Asp	Gln	Val	75 Ser 90
35	Tyr Ala	Lys Val	Glu	Arg Ser	Tyr 80 Tyr 95	Leu Tyr	Phe Tyr	Val Asp	Tyr Asp	70 Arg 85 Gly 100	Pro Cys	Asp Glu	Gln Pro	Val Cys	75 Ser 90 Gly 105

	Ala	Pro	Gly	Asp	Ala \ 140	Jal 1	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr		Val 150
	Tyr	Leu	Asp	Val	Gln (Glu :	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Le u 165
5	Met	Gly	Asp	Phe	Asn 2	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg :	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	INFC	RMAT	NOI	FOR S	SEQ :	ID N	0:47	:						
20	((A) L B) T	ENGT	CHARA H: 26 Amir OGY:	50 at	mino cid		ds						
	(×	i) S	EQUE	ENCE	DESCI	RIPT	ION:	SEC	ID	NO:4	7:				
25	Leu 1	_	s Ile	e Ala	Ala 5	Phe	Asn	Ile	: Glr	Thr 10		e Gly	/ Glu	Thr	Lys 15
	Met	Sei	r Ası	n Ala	Thr 20	Leu	Val	Ser	Туі	25		Glr	ı Ile	Leu	Ser 30
3 C	Arg	ту:	r Ası	p Ile	e Ala 35		. Val	Glr	ı Glı	ı Val		g Asp	Ser	His	Leu 45
	Thr	Al.	a Vai	1 G1;	y Lys 50		Lev	ı Ası	o Ası	n Let		e Gli	n Asp	Ala	Pro 60
	Ası	Th.	r Ty	r Hi	s Tyr 65		. Val	l Se	r Gl	u Pro		u Gl	y Arg	J Asr	Ser 75
35	Ту	r Ly	s Gl	u Ar	g Tyr 80		ı Phe	e Va	l Ty	r Ar		o As	p Gli	ı Val	Ser 90
	1A	a Va	1 As	n Se	r Tvr	TVI	r Ty:	r As	D As	p Gl	y Cy	s Gl	u Pro	o Cys	s Gly

	ıeA	ı As	p Thi	Phe	Asn 110	Arg	Glu	Pro	o Ala	a Ile 115	Val	Arg	J Phe	e Phe	Ser 120
	Arg	g Ph	e Thr	Glu	Val 125	Arg	Glu	Phe	≥ Ala	a Ile 130		Pro	Leu	His	Ala 135
5	Ala	Pr	o Gly	Asp	Ala 140	Val	Ala	Glu	ı Ile	2 Asp	Ala	Leu	Tyr	Asp	Val 150
	Туг	Lei	u Asp	Val	Gln 155	Glu	Lys	Trp	Gly	' Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met	Gly	y Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Туг 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Sei	r Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
15	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
20	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
				ON F					:						
25	` -	(. (:	A) LE B) TY	ENGTH PE: .	: 26 Amin	0 am	inc id	CS: acid	is						
	(xi	.) s	EQUEN	ICE D	ESCR:	IPTI	O N :	SEQ	ID N	10 : 48	:				
30	Leu 1	Lys	Ile	Ala	Ala 1 5	Phe .	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala :	Thr I	Leu '	Val :	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile A	Ala I 35	Leu 1	Val (Gln	Glu	Val .	Arg .	Asp	Ser :	His	Leu 45
35	Thr	Ala	Val	Gly 1	-ys I 50	Leu I	Leu 1	Asp	Asn	Leu 1	Ľys (Gln /	Asp /	Ala	Prc 60
	qsA	Thr	Tyr	His T	Cyr V 65	/al \	al S	Ser	Glu	Pro 1	Leu (Gly A	Arg i	Asn .	Ser 75

	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90	•
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105	, 5
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120	5
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 139	a 5
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Va:	1 0
	Туr	Leu	Asp	Val	Gln 155		Lys	Trp	Gly	Leu 160		Asp	Val	Met	Le	u 5
	Met	Gly	Asp	Phe	170		Gly	Cys	Ser	Tyr 175		Arg	Pro	Sei	Gl 18	n 0
15	Trp	Ser	Ser	Ile	Arg		Trp	Thr	Ser	Pro 190		Phe	Glr	n Try	19	u 5
	Ile	Pro	Asp	Ser	Ala 200		Thr	Thr	Ala	205		Thi	Hi:	в Су	s Al 21	а .0
20	Ту	c Ası	p Arg	g Ile	e Val		l Ala	a Gly	/ Met	220		ı Arg	g Gl	y Al	a Va 22	1 2 5
	Va?	l Pro	o As	p Se	r Ala 23		u Pro	phe	e Ası	n Pho 23	e Gl:	n Ala	a Al	а Ту	r Gl 24	10 7
	Le	u Se	r As	p Gl	n Le		a Gl:	n Ala	a Il	e Se 25	r As	рНі	ѕ Ту	r Pr	o Va 25	al 55
25	Gl	u Va	l Me	t Le	u Ly 26											
	(2)	INF	ORMA	TION	FOR	SEQ	ID	NO : 4	9:							
30		(i)	(A) (B)	LENG TYPE	E: An	260 nino	ERIS amin Acid	o ac	: :ids							
		(xi)	SEQU	JENCI	E DES	SCRIE	OITS	I: SE	EQ II	NO:	49:					
	Le	eu Ly 1	ys I	le A	la A	la Pi 5	ne As	sn Il	le Gl		nr Pl	ne G	ly G	lu T	hr L	ys 15
35	M	et S	er A	sn A		hr L	eu Va	al Se	er T	yr I	le Va 25	al G	ln I	le L	eu S	Ser 30
	A	rg T	yr A	sp I		la L 35	eu V	al G	ln G		al A 40	rg A	sp S	er H	is I	Leu 45

	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Arg	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Туг 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
15	туг	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Glγ	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	qeA	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
30	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT	ION :	FOR	SEQ	ID N	0:50	:						

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH 260 amino acids
 - (B) TYPE: Amino Acid
- 35 (D) TOPOLOGY: Linear
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:50.

Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys
1 5 10 15

	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
5	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Trp	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
10	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	Hıs	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	Asp	Ser	Ala 230		Pro	Phe	Asn	Phe 235		Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245		Gln	Ala	Ile	Ser 250		His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

35 (2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amino Acid
 - (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

	Lei	ı Lv	s Ile	- Ala	4 A 1 a	a Dhe			- 01						
	4				-	•				10)				r Lys 15
5	Met	Se:	r Ası	n Ala	Thr 20	Leu	Val	. Ser	Туг	r Ile 25		Gln	Ile	e Let	Ser 30
	Arg	Ty:	r Ası	> Il∈	Ala 35	Leu	Val	Gln	ı Glu	val 40	Arg	Asp	Ser	His	4.5
	Thr	Ala	a Val	. Gly	Lys 50	Leu	Leu	Asp	Asr	Leu 55		Gln	Asp	Ala	Pro 60
10	Asp	Thi	туг	His	Cys 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asr	Ser 75
	Tyr	Lys	5 Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
25	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
3 0	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu .	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln .	Ala	Ala	Tyr	Gly 240
35	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His '	Tyr	Pro	Val 255
	Glu	Val	Met		Lys 260										
	101 -														

(2) INFORMATION FCR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 260 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

5	(xi) SE	QUEN	CE DI	ESCR	IPTI	ON: :	SEQ	ID N	0:52	:				
	Leu 1	Lys	Ile	Ala i	Ala 1 5	Phe .	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala '	Thr :	Leu	Val	Ser	Тут	Ile 25	Val	Gln	Ile	Leu	Ser 30
10	Arg	Tyr	Asp	Ile .	Ala:	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
15	Asp	Thr	Tyr	His	Lys 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
20	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e 130	Val	Pro	Leu	His	Ala 135
25	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	: Gly	/ Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175		Arg	Pro	Ser	Gln 180
30	Trp	Sei	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190		Phe	Glr	Trp	195
	116	e Pro	Asp	Ser	Ala 200		Thr	Thi	Ala	Thr 205		Thr	His	s Cys	210
35	Ту	r Asj	p Arg	g Ile	Val 215		Ala	Gly	y Met	220		Arg	g Gly	y Ala	225
	Va.	l Pr	o Ası	Ser	230		ı Pro	Phe	e Asr	n Phe 235		n Ala	a Ala	а Туі	Gly 240
	Le	u Se	r Asj	p Glr	Leu 245		a Glr	a Ala	a Ile	250		Hi:	з Ту	r Pro	255

Glu Val Met Leu Lys 260

5

(2) INFORMATION FOR SEQ ID NO:53:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:53:

10	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Le u 4 5
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Le u 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Met 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
30	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
35	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225

Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly 235 Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val 250 Glu Val Met Leu Lys (2) INFORMATION FOR SEQ ID NO:54: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 260 amino acids (B) TYPE: Amino Acid 10 (D) TOPOLOGY: Linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:54: Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser 15 Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro 2.0 Asp Thr Tyr His Ser Val Val Ser Glu Pro Leu Gly Arg Asn Ser Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser 25 Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 30 Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu 160 35 Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln 170 175 Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 185 190

	Ile	Pro	Asp	Ser	200	Asp	Thr	Thr	Ala	a Thi 209		Thi	His	s Cys	3 Ala 210
	Tyr	Asp	Arg	; Ile	215	. Val	Ala	Gl _}	' Met	220		Arg	g Gly	⁄ Ala	Val 225
5	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	: Asr	n Phe 235		Ala	a Ala	туг	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	250		His	Tyr	Pro	Val 255
10	Glu	Val	Met	Leu	Lys 260										
	(2)	INFC	RMAT	ION	FOR	SEQ	ID N	0:55	:						
15		(A) L B) T D) T	ENGT YPE : OPOL	H: 2 Ami OGY:	ACTE 60 a no A Lin	mino cid ear	aci							
	(x	i) S	EQUE	NCE	DESC	RIPT	ION:	SEQ	ID	NO: 5	5:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
20	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
25	Asp	Thr	Tyr	His	Tyr 65	Val	Cys	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	туr	Arg 85	Pro	Asp	Gln	Val	Ser 90
30	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
35	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165

	Met	Gly	Asp	Phe	Asn . 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg :	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile	Pro	Asp	Ser	Ala 200	qeA	Thr	Thr	Ala	Thr 205	Prc	Thr	Hıs	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
10	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
15	(2)	INFO	RMAT	ION	FOR S	EQ 1	D NO	56:56	:						
20		((A) L B) T D) T	ENGT YPE : OPOL	CHARA H: 26 Amir OGY: DESCI	0 ar 10 Ac Line	mino cid ear	aci		N O : 5	6:				
	Lou	. T.v.	, Tle	בומ	Ala	Dhe	Asn	Tle	Gln	Thr	Phe	Glv	, Glu	Thr	Lvs
	1			•••	5					10		•			15
	Met	: Sei	r Asn	Ala	Thr 20	Leu	Val	Ser	Туг	Ile 25		Gln	ılle	Leu	Ser 30
25	Arg	у Ту	r Asp	lle	Ala 35	Leu	Val	Gln	Glu	Val		asp	Ser	His	Leu 45
	Thi	r Ala	a Val	. Gly	Lys 50	Leu	Leu	Asp	Asr	Leu 55		n Glr	n Asp	Ala	Pro 60
30	As	p Th	r Ty	His	Tyr 65		Asp	Ser	Gli	1 Pro 70		ı Gly	y Arg	g Asr	Ser 75
	ту	r Ly	s Gl	ı Arç	Tyr 80		Phe	· Val	Туг	r Arg		o Ası	p Glr	n Val	. Ser 90
	Al	a Va	l As	p Sei	r Tyr 95		Туг	Asp	As _l	0 Gly		s Gl	u Pro	o Cys	5 Gly 105
35	As	n As	p Th	r Ph	e Asr		g Glu	ı Pro	o Al	a Il.		l Ar	g Ph	e Phe	ser 120
	Ar	g Ph	ie Th	r Gl	u Val		g Glu	ı Phe	e Al	a Il		l Pr	o Le	u Hi	s Ala 135

					11	,				14	5				Val 150
	Ţγ	r Le	eu As	sp Va	l Glr 159	ı Glı	ı Lys	Tr	p Gl	y Let 160	u Glu C	Asp	Val	Met	Leu 165
5	Me	t G1	y As	p Ph	e Asr	Ala	Gly	′ Cy:	s Se	r Tyi	val	Arg	Pro	Ser	Gln 180
	Tr	p Se	er Se	r Ile	e Arg	. Leu	Trp	Thi	r Se	r Pro	Thr	Phe	Gln	Trp	Leu 195
10	Il	e Pr	o As	p Se	r Ala 200	Asp	Thr	Thi	Ala	a Thr 205	Pro	Thr	His	Cys	Ala 210
	ту	r As	p Ar	g Il€	215	Val	Ala	Gly	/ Mei	t Leu 220	Leu	Arg	Gly	Ala	Val 225
	Va	l Pr	o As _l	p Ser	230	Leu	Pro	Phe	. Ası	n Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Le	ı Se	r Ası	9 Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Gli	ı Va	l Met	Leu	Lys 260										
	(2)	INFO	ORMAT	TION	FOR S	SEQ :	ID NO): 5 7	:						
20	•	((A) L (B) T	ENGT YPE :	CHARA H: 26 Amir OGY:	50 ап 10 Ас	nino cid	CS: aci	ds						
	(x	i) S	EQUE	NCE 1	DESCR	IPTI	: NO	SEQ	ID :	NO:57	' :				
25	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly (Glu ′	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln :	Ile I	Leu .	Ser 30
30	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg /	Asp S	Ser F	His :	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu :	Leu i	Asp	Asn	Leu . 55	Asn (Gln A	Asp A	ala 1	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val 1	His S	Ser	Glu	Pro :	Leu (Gly A	arg A	sn S	Ser 75
35	Tyr	Lys	Glu	Arg	Tyr 1	Leu I	Phe V	/al	Tyr	Arg 1	Pro A	Asp G	ln V	al S	Ser 90
	Ala	Val	Asp	Ser	Tyr 1	Tyr J	ſyr <i>Þ</i>	Asp .		Gly (Cys G	Slu P	ro C		17 05

	Asn	Asp	Thr	Phe	Asn	Arg	Glu	Pro	Ala	11e	Val	Arg	Phe	Phe	120	
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e 130	Val	Pro	Leu	His	Ala 135	
5	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp	Ala	Leu	Tyr	Asp	Val 150	
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165	
10	Met	Gly	Asp	Phe	As n 170	Ala	Gly	Cys	Ser	T yr	Val	Arg	Pro	Ser	Gln 180	
	Trp	Ser	Ser	Ile	Arg 185		Trp	Thr	Ser	Pro 190		Phe	Gln	Trp	Leu 195	
	Ile	Pro	Asp	Ser	Ala 200		Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210	
15	Tyr	Asp	Arg	Ile	. Val		Ala	Gly	Met	Leu 220		Arg	g Gly	/ Ala	Val 225	
	Val	Pro	Asp	Ser	230		ı Pro	Phe	Asn	235	e Glr	a Ala	a Alá	а Туг	Gly 240	,)
20	Lev	se:	r Asp	Glr	1 Let 24!		a Gln	Ala	Ile	250	Asp	Hi	з Ту	r Pro	val 255	>
	Glı	ı Vai	l Met	t Lev	а Б уя											
	(2)	INF	orma'	TION	FOR	SEQ	ID 1	10 : 56	3:							
25		(i)	(A) (B)	LENG TYPE	TH: : Am											
	(xi)	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	N O:	58:					
30	Le	u Ly 1	s Il	e Al	a Al	a Ph	e As	n Il	e Gl		ir Ph	e Gl	y Gl	u Th	ır Ly 1	s
	Me	t Se	er As	sn Al		ır Le 20	u Va	l Se	г Ту		e Va 25	ıl Gl	ın Il	e Le	eu Se 3	0
	Aı	g Ty	yr As	sp Il		la Le 35	eu Va	ıl Gl	n Gl		al Ar 10	g As	sp Se	er H	is Le	e u 15
35	Tì	ır A	la Va	al G		ys Le 50	eu L€	eu As	sp As	sn Le	eu As 55	sn G	ln A	sp A	la Pr	50
	A:	sp T	hr T	yr H		yr V 65	al Me	et Se	er G	lu P	rc Lo	eu G	ly A	rg A	sn Se	er 75

	Tyr Lys G	u Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala Val As	sp Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn Asp Th	ir Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg Phe Th	ır Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala Pro Gl	y As p	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr Leu As	p Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met Gly As	p Phe	As n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp Ser Se	r Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile Pro As	p Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr Asp Ar	g Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val Pro As	p Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu Ser As	p Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
25	Glu Val Me	t Leu	Lys 260										
	(2) INFORMA	TION I	FOR S	SEQ 1	D NO):59:	:						
30	(B)	ENCE (LENGTH TYPE: TOPOL(∃: 2€ Amir	50 an	nino		ls						
	(xı) SEQU	ENCE I	DESCR	RIPTI	: NO	SEQ	ID 1	10 : 5 9	:				
	Leu Lys Il 1	e Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
35	Met Ser As	n Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg Tyr As	p Ile	Ala 35	Leu	Val	Gln	Glu	Val	Arg	Asp	Ser	His	Leu 45

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	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Pro	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
E 5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230		Pro	Phe	Asn	Phe 235		Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245		Gln	Ala	Ile	Ser 250		His	Tyr	Pro	V al 255
30	Glu	Val	. Met	Leu	Lys 260										
	(2)	TNEC	ר א א סר	TON	FOR	SEO	TD N	n · 6 n	١.						

- (2) INFORMATION FOR SEQ ID NO:60:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amino Acid
- 35 (D) TOPOLOGY: Linear
 - (x1) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys 10

	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
5	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Arg	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
10	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	туг	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	11e 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Le u 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

35 (2) INFORMATION FOR SEQ ID NO:61:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amino Acid
 - (D) TOPOLOGY: Linear

(x:)	SECUENCE	DESCRIPTION:	C EO	TD	NO.CI
1~+/	SPOOPIACE	DESCRIPTION:	SEU	11)	NO:61:

	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	His	Tyr 65	Val	Ser	Ser	Glu	Pro 70	Leu	Gly	Arg	neA	Ser 75
					8 C		Phe			85					90
15					95		Tyr			100					105
					110		Glu			115					120
					125		Glu			130					135
20					140		Ala			145					150
					155		Lys			160					165
25					170		Gly			175					180
					185		Trp			190					195
20					200		Thr			205					210
30					215		Ala			220					225
					230		Pro			235					240
35					245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 260 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

			02001										
5			ICE DES										
	Leu Ly 1	s Ile	Ala Ala	a Phe 5	Asn	Ile	e Glr	Thr		Gly	Gli	ı Th:	r Lys 15
	Met Se	r Asn	Ala Thi	r Leu	Val	Ser	Туг	: Ile 25	Val	Gln	Ile	. Le	Ser 30
10	Arg Ty	r Asp	Ile Ala	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	45
	Thr Al.	a Val	Gly Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
15	Asp Th	r Tyr	His Tyr 65	Val	Val	Lys	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr Lys	s Glu i	Arg Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala Val	Asp S	Ser Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
20	Asn Asp	Thr I	Phe Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg Phe	Thr (Glu Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
25	Ala Pro	Gly A	Asp Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr Leu	Asp V	al Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu .	Asp	Val	Met	Leu 165
	Met Gly	Asp P	he Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val .	Arg	Pro	Ser	Gln 180
30	Trp Ser	Ser I	le Arg 185	Leu '	Trp	Thr	Ser	Pro 190	Thr 1	Phe (Gln	Trp	Leu 195
	Ile Pro	Asp S	er Ala 200	Asp :	Thr '	Thr	Ala	Thr :	Pro :	Thr 1	His	Cys	Ala 210
35	Tyr Asp	Arg I	le Val 215	Val A	Ala (Gly .		Leu 1 220	Leu A	Arg (Gly .	Ala	Val 225
	Val Pro	Asp S	er Ala 230	Leu F	Pro I	Phe .		Phe (235	Gln A	Ala A	Ala	Tyr	Gly 240
	Leu Ser	Asp G	ln Leu 245	Ala G	3ln A	Ala :		Ser # 250	Asp H	lis T	fyr :		Val 255

Glu Val Met Leu Lys 260

5

(2) INFORMATION FOR SEQ ID NO:63.

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 260 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:63:

10	Leu 1	Lys	Ile	Ala .	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Met	Glu	Pro 70	Leu	Gly	Arg	Asn	ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arç	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	a Pro	Gly	/ Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
30	ту	r Lei	ı Asp	Val	Gln 155		Lys	Trp	Gly	/ Leu 160		Asp	Val	Met	Leu 165
	Me	t Gly	y Ası	p Phe	170		Gly	Суз	s Ser	Tyr 175		Arg	Pro	Ser	Gln 180
	Tr	p Se:	r Se:	r Ile	Arg		Trp	Th:	s Sei	190		Phe	Glr	Trp	195
35	Il	e Pr	o As	p Ser	Ala 200		o Thr	Thi	r Ala	a Thi 205		Thr	His	s Су:	s Ala 210
	Ту	r As	p Ar	g Ile	e Val		l Ala	a Gly	y Mei	t Lei 220		ı Arg	g Gl	/ Ala	a Val 225

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WO 96/26279 PCT/US96/02421 Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val Glu Val Met Leu Lys (2) INFORMATION FOR SEQ ID NO:64: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 260 amino acids 10 (B) TYPE: Amino Acid (D) TOPOLOGY: Linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64: Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser 15 Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu

Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro 50 55 60

Asp Thr Tyr His Tyr Val Val Arg Glu Pro Leu Gly Arg Asn Ser

65 70 This lyr Val Val Arg Glu Pro Leu Gly Arg Asn Ser

Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser 80 85 90

25 Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly 95 100 105

Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser

Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala

30

Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 140 145 150

Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu 155 160 165

Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln 170 175 180

Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 185 190 195

	Ile F	Pro	Asp	Ser	Ala 200	Asj	r Tì	nr T	hr	Ala	20	r P:	ro T	hr'	His	C	/S P 2	la !10
	Tyr A	Asp	Arg	Ile	Val 215		1 A	la (Sly	Met	2 Le	u L	eu A	ırg	Gly	A	la V	/al 225
5	Val 1	Pro	Asp	Ser	Ala 230		u P	ro l	Phe	Ası	n Ph 23	ie G 35	ln A	Ala	Ala	T	yr (Gly 240
	Leu :	Ser	Asp	Gln	Lev 245		a G	ln .	Ala	Il	e Se 25	er A	.sp 1	His	Туг	P	ro '	Val 255
10	Glu	Val	Met	Leu	Lys 260													
	(2) I	иfо	RMAT	NOI	FOR	SEÇ) II	NC	:65	:								
15	(i	(A) I B) T (D) T	ENGT TYPE TOPO	CHAI TH: : Am LOGY	260 ino : L:	ami Aci inea	ino id ar	aci									
	(xi				DES													
	Leu 1	Lys	s Ile	e Al	a Al	a P 5	he i	Asn	Ile	e G:	ln T	hr 10	Phe	Gly	y Gl	u 1	Thr	Lys 15
20	Met	Se	r As	n Al	a Th	r L	eu	Val	Se	r T	yr 1	le 25	Val	Gl	n Il	е :	Leu	Ser 30
	Arg	ту	r As	p Il		.a L 35	eu	Val	Gl	n G	lu V	Val 40	Arg	As	p Se	er	His	Leu 45
	Thr	Al	a Va	.1 G1		ys I 50	_eu	Leu	As	рA	sn 1	Leu 55	Asn	G1	n As	sp	Ala	Pro 60
25	Asp	Th	т Ту	r H		yr \ 65	Jal	Val	Se	r A	la	Pro 70	Leu	Gl	у А:	rg	Asn	Ser 75
	туг	. Ly	s Gl	Lu A:		yr 1 80	Leu	Phe	e Va	l T	Cyr	Arg 85	Pro	As	p G	ln	Val	Ser 90
30	Ala	a Va	al A	sp S	er T	yr 95	Tyr	ту	c As	sp A	Asp	Gly 100	Cys	; G]	lu P	ro	Суя	: Gly 105
	Ası	n As	sp T	hr P		sn 10	Arg	Gl.	u Pi	ro i	Ala	Ile 115	Va:	l A:	rg F	he	Phe	120
	Ar	g P	he T	hr G		/al	Arg	Gl	u P	he .	Ala	11e	Va:	1 P	ro I	eu	Hi	s Ala 135
35	Al	a P	ro G	ly F		Ala 140	Val	Al	a G	lu	Ile	Asp	Al	a L	eu :	ſyr	As	p Val 150
	ту	r L	eu A	sp '	Jal (Gln	Gli	а Lу	s T	rp	Gly	Le:	ı Gl	u A	.sp	val	Me	t Leu 165

		GIŞ	Asp	Pne	170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
10	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
15	(2)	INFO	TAMS	ION I	FOR S	SEQ :	ID N	0:66	:						
	į)	() ()	3) TY	ENGTI YPE :		50 ar 10 Ad	mino cid		i s						
20	(xi	i) SI	EQUE	NCE I	DESC	RIPT	ION:	SEQ	ID 1	10 : 6	5 :				
20			EQUEN									Gly	Glu	Thr	Lys 15
20	Leu 1	Lys		Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe				15
20	Leu 1 Met	Lys Ser	Ile	Ala Ala	Ala 5 Thr 20	Phe Leu	A sn Val	Ile	Gln Tyr	Thr 10 Ile 25	Phe Val	Gln	Ile	Leu	15 Ser 30
	Leu 1 Met	Lys Ser Tyr	Ile	Ala Ala Ile	Ala 5 Thr 20 Ala 35	Phe Leu Leu	Asn Val Val	Ile Ser Gln	Gln Tyr Glu	Thr 10 Ile 25 Val 40	Phe Val Arg	Gln	Ile	Leu His	15 Ser 30 Leu 45
	Leu 1 Met Arg	Lys Ser Tyr Ala	Ile Asn Asp	Ala Ala Ile	Ala 5 Thr 20 Ala 35 Lys 50	Phe Leu Leu	Asn Val Val Leu	Ile Ser Gln Asp	Gln Tyr Glu Asn	Thr 10 Ile 25 Val 40 Leu 55	Phe Val Arg Asn	Gln Asp Gln	Ile Ser Asp	Leu His Ala	15 Ser 30 Leu 45 Pro 60
25	Leu 1 Met Arg Thr	Lys Ser Tyr Ala	Ile Asn Asp	Ala Ala Ile Gly	Ala 5 Thr 20 Ala 35 Lys 50 Tyr 65	Phe Leu Leu Val	Asn Val Val Leu	Ile Ser Gln Asp	Gln Tyr Glu Asn Cys	Thr 10 Ile 25 Val 40 Leu 55 Pro 70	Phe Val Arg Asn Leu	Gln Asp Gln	Ile Ser Asp	Leu His Ala Asn	15 Ser 30 Leu 45 Pro 60 Ser 75
25	Leu 1 Met Arg Thr Asp	Lys Ser Tyr Ala Thr	Ile Asn Asp Val	Ala Ile Gly His	Ala 5 Thr 20 Ala 35 Lys 50 Tyr 65 Tyr 80	Phe Leu Leu Val	Asn Val Val Leu Val	Ile Ser Gln Asp Ser	Gln Tyr Glu Asn Cys	Thr 10 Ile 25 Val 40 Leu 55 Pro 70 Arg 85	Phe Val Arg Asn Leu Pro	Gln Asp Gln Gly	Ile Ser Asp Arg	Leu His Ala Asn Val	15 Ser 30 Leu 45 Pro 60 Ser 75 Ser 90
25	Leu 1 Met Arg Thr Asp Tyr	Lys Ser Tyr Ala Thr Lys Val	Ile Asn Asp Val Tyr	Ala Ala Ile Gly His Arg	Ala 5 Thr 20 Ala 35 Lys 50 Tyr 65 Tyr 80 Tyr 95	Phe Leu Leu Val Leu Tyr	Asn Val Val Leu Val Phe	Ile Ser Gln Asp Ser Val	Gln Tyr Glu Asn Cys Tyr Asp	Thr 10 Ile 25 Val 40 Leu 55 Pro 70 Arg 85 Gly 100	Phe Val Arg Asn Leu Pro Cys	Gln Asp Gln Gly Asp	Ile Ser Asp Arg Gln	Leu His Ala Asn Val	15 Ser 30 Leu 45 Pro 60 Ser 75 Ser 90 Gly

	Ala	Prc	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	As p 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
5	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Суѕ	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMATI	ON I	FOR S	SEQ :	ID NO	0:67	:						
									-						
20	(:	i) SI () (I	EQUEN A) LI B) TY	NCE (ENGTI (PE:		ACTEI	RIST: mino cid	ICS:							
20		i) SI () (I	EQUEN A) LI B) TY	NCE (ENGTI (PE:	CHARA H: 26 Amir OGY:	ACTEI 50 an no Ac Line	RIST: mino cid ear	ICS: acio	is	[™] O:6	7:				
20	(x:	i) SI (J (I	EQUEN A) LE B) TY D) TO	NCE (ENGTH (PE: DPOL(CHARA H: 26 Amir DGY:	ACTEI 50 an 10 Ac Line	RIST:	ICS: acid	is			Gly	Glu	Thr	Lys 15
	(x: Leu 1	i) SI (<i>I</i> (I (I	EQUER A) LE B) TY D) TO EQUER	NCE (PE:DPOLG	CHARI H: 26 Amir DGY: DESCR Ala 5	ACTEI 50 am no Ao Line RIPT:	RIST: mino cid ear ION:	ICS: acid SEQ	is ID I Gln	Thr 10	Phe				15
	(x: Leu 1 Met	i) SI (I (I (I Lys	EQUENA) LE A) LE B) TO C) TO EQUEN Ile Asn	NCE (PE: DPOLO NCE I Ala	CHARI H: 26 Amir DGY: DESCE Ala 5 Thr 20	ACTEI 50 ar no Ao Line RIPT: Phe	RIST: mino cid ear ION: Asn	ICS: acid SEQ Ile Ser	is ID I Gln Tyr	Thr 10 Ile 25	Phe Val	Gln	Ile	Leu	15 Ser 30
25	(x: Leu 1 Met	i) SE (I) (I) (I) Lys Ser	EQUER A) LE B) TY D) TO EQUER Ile Asn Asp	NCE (ENGTH) (PE: OPOLO NCE I Ala Ala Ile	CHARD H: 26 Amir DGY: DESCR Ala 5 Thr 20 Ala 35	ACTEI 50 an 10 Ac Line RIPT: Phe Leu	RIST: mino cid ear ION: Asn Val	ICS: acid SEQ Ile Ser	is ID I Gln Tyr	Thr 10 Ile 25 Val 40	Phe Val Arg	Gln Asp	Ile Ser	Leu	15 Ser 30 Leu 45
25	(x: Leu 1 Met Arg	i) Si (I (I i) Si Lys Ser	EQUER A) LH B) TY D) TO EQUER Ile Asn Asp	NCE (ENGTHER) POLO NCE I Ala Ala Ile	CHARACTER OF THE TOTAL THE T	ACTEI 50 an 10 Ac Line RIPT: Phe Leu Leu	RIST: mino cid ear ION: Asn Val Val	SEQ Ile Ser Gln Asp	is ID i Gln Tyr Glu Asn	Thr 10 Ile 25 Val 40 Leu 55	Phe Val Arg	Gln Asp Gln	Ile Ser Asp	Leu His	15 Ser 30 Leu 45 Pro 60
25	Leu 1 Met Arg Thr	i) Si (I (I i) Si Lys Ser Tyr	EQUER A) LH B) TY D) TO EQUER Asn Asp Val	NCE (ENGTHER PROBLEM P	CHARACTER OF THE CONTROL OF THE CONT	ACTEI 50 ar 10 Ac Line RIPT: Phe Leu Leu	RIST: mino cid ear ION: Asn Val Val Leu Val	SEQ Ile Ser Gln Asp	is ID i Gln Tyr Glu Asn	Thr 10 Ile 25 Val 40 Leu 55 Pro 70	Phe Val Arg Asn	Gln Asp Gln Gly	Ile Ser Asp	Leu His Ala Asn	15 Ser 30 Leu 45 Pro 60 Ser 75

	Ası	ı As	p Thi	Phe	Asn	Arg	Glu	Pro) Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Ph	e Thr	- Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
5	Ala	Pro	o Gly	Asp	Ala 140	Val	Ala	Glu	lle	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Lei	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10					170					175					Gln 180
				Ile	185					190					195
				Ser	200					205					210
15				Ile	215					220					225
				Ser	230					235					240
20				Gln	245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
				Leu	260										
25		i) s. (. (:	EQUEN A) LE B) TY	ON F ICE C ENGTH PE:	HARA : 26 Amin	CTER 0 am 0 Ac	ISTI ino id	CS:							
	(xi	.) s:		ICE D				SEQ	ID N	O:68	:				
30	Leu 1	Lys	Ile	Ala .	Ala : 5	Phe .	Asn	Ile	Gln	Thr :	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala '	Thr 1 20	Leu '	Val:	Ser	Tyr	Ile Y 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile A	Ala 1 35	Leu '	Val (Gln	Glu	Val 2 40	Arg .	Asp :	Ser 1	His	Leu 45
35	Thr	Ala	Val	Gly I	Lys I 50	Leu 1	Leu A	Asp .	Asn :	Leu <i>I</i> 55	Asn (Gln A	Asp A	Ala	Pro 60
	Asp	Thr	Tyr	His 7	Tyr 1 65	/al \	Val S	Ser	Glu 1	Pro I 70	Jeu (Gly A	Arg 1	Asn	Ser 75

	туr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	90
	Ala	Val	Asp	Ser	T yr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Сув	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	As p	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155		Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	' Asp	Phe	Asn 170		Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp	Ser	s Ser	Ile	189		Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	o Asp	Ser	Ala 200		Thr	Thr	Ala	205		Thr	His	Cys	Ala 210
20	Туз	c As	p Arg	g Ile	e Val		i Ala	a Gly	/ Met	220	Leu	Arg	g Gly	Ala	Val 225
	Va:	l Pr	o Ası	p Se	r Ala 23		ı Pro	> Phe	e Ası	n Phe 235	e Gln	Ala	a Ala	туг	Gly 240
	Le	u Se	r As	p Gl:	n Le		a Gl	n Al	a Il	e Sei 250	Asp	His	s Туг	r Pro	255
25	Gl	u Va	l Me	t Le	u Ly 26										
	(2)	INF	ORMA	MOIT	FOR	SEQ	ID	NO : 6	9:						
30		(i)	(B)	LENG TYPE	TH: : An	RACT 260 nino (: Li	amin Acid	o ac I	: :1ds						
	((xi)	SEQU	ŒNCE	E DES	SCRIF	10IT	: SE	EQ II	NC:	69:				
	L€	eu Ly 1	ys Il	le Al	la Al	la Ph 5	ne As	n Il	le Gl		r Ph	e Gl	y Gl	u Th	r Lys 15
35	Me	et S	er A	sn Al		hr Le 20	eu Va	al Se	er Ty	yr Il	e Va 25	.1 G1	ln Il	e Le	eu Ser 30
	A	rg T	yr A	sp I		la L 35	eu V	al G	ln G		al Ar 10	g As	sp Se	er Hi	ıs Lei 45

	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	туr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Туr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Glu	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Aap	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	туr	Pro	Val 255
3 0	Glu	Val	Met	Leu	Lys 260										
	(2) I	NFOF	ITAMS	ON F	FOR S	EQ I	D NO	:70:							
	(i		EQUEN												
			A) LE B) TY					acid	is						
3 5			o To												

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:
- Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys 10

	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
5	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
10	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Туr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Gly	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	As p		Leu	Tyr	Asp	Val 150
20	-			Val	155					160					165
				Phe	170					175					180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190		Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205		Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215		Ala	Gly	Met	220		Arg	Gly	Ala	. Val 225
30	Val	Pro) Asp	Ser	Ala 230		Pro	Phe	Asr	235		n Ala	Ala	туг	Gly 240
	Leu	Sei	Asp	Gln	Leu 245		Gln	Ala	ı Ile	250		His	туг	Pro	255
	Glu	ı Val	l Met	. Leu	. Lys 260										

- 35 (2) INFORMATION FOR SEQ ID NO:71:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amino Acid
 - (D) TOPOLOGY: Linear

(xi)	SEQUENCE	DESCRIPTION:	SEQ	ID	NO:71:
------	----------	--------------	-----	----	--------

	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Hıs	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	His	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
25	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
30	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
35	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 260 amino acids (B) TYPE: Amino Acid (D) TOPOLOGY: Linear (x1) SEQUENCE DESCRIPTION: SEQ ID NO:72: 5 Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys 5 Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu 10 Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn Ser 15 Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly 100 95 Asn Asp Thr Phe Asn Arg Glu Pro Lys Ile Val Arg Phe Phe Ser 20 115 110 Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 130 Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 25 Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 30 Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala 205 200

220

250

Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Val

Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly

Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val

35

Glu Val Met Leu Lys 260

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEO ID NO:73:

	(X1)	SEQUENC	E DESCRI	PTION	: SEC	QI Q	N O : 7	3 :				
10	Leu Ly 1	s Ile A	la Ala P 5	he Ası	n Ile	e Glr	Thr	Phe	Gly	Glu	u Th	r Lys 15
			a Thr L 20				25					30
			e Ala L				40					45
15			y Lys Lo 50				55					60
			s Tyr Va 65				70					75
20			g Tyr Le 80				85					90
			r Tyr Ty 95				100					105
0.5			≥ Asn Ar 110				115					120
25			val Ar 125				130					135
			Ala Va 140				145					150
30			Gln Gl				160					165
			Asn Ala				175					180
35	Trp Ser		103				190					195
<i></i>	Ile Pro		200			:	205					210
	Tyr Asp	Arg Ile	Val Val 215	Ala	Gly I	Met 1	Leu L 220	eu A	rg (Sly A		Val 225

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WO 96/26279

	Val Pro A	Asp Ser	Ala L 230	eu P	ro P	he A	sn Pl	he Gl 35	ln A	la A	la T	yr G 2	1 y 4 0
	Leu Ser l	Asp Gln	Leu A 245	la G	ln A	la I	le S	er A: 50	sp H	ıs T	yr P	ro V	'al 55
5	Glu Val I	Met Leu	Lys 260										
	(2) INFOR	NOITAM	FOR SE	EQ ID	NO:	74:							
10	(A (B	QUENCE () LENGT () TYPE: () TOPOI	H: 260 Amin	o ami	ino a		5						
	(xi) SE	QUENCE	DESCR	IPTIC	ON: 5	SEQ	ID NO	0:74:					
	Leu Lys 1	Ile Ala	a Ala 5	Phe 1	Asn	Ile	Gln '	Thr I	?he (Gly (Glu '	Thr	Lys 15
15	Met Ser	Asn Al	a Thr 20	Leu	Val	Ser	Tyr	lle V 25	/al	Gln	Ile	Leu	Ser 30
	Arg Tyr	Asp Il	e Ala 35	Leu	Val	Gln	Glu	Val :	Arg	Asp	Ser	His	Leu 45
20	Thr Ala	Val Gl	y Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp Thr	туг Ні	s Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr Lys	Glu Ai	rg Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
25	Ala Val	Asp S	er Tyr 95		Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn Ası	o Thr P	he Asn 110		Glu	Pro	Met	Ile 115	Val	Arg	Phe	Phe	Ser 120
30	Arg Ph	e Thr G	lu Val 125		Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	135
	Ala Pr	o Gly A	sp Ala		Ala	Glu	ılle	Asp 145	Ala	Leu	туг	Asp	Val 150
	Tyr Le	u Asp \	al Gli 15		ı Lys	Trp	o Gly	, Leu 160	Glu	. Asp	o Val	Met	. Leu 165
35	Met Gl	y Asp I	Phe As:	n Ala O	a Gly	у Су:	s Sei	Tyr 175	Val	Arg	g Pro	o Se	r Glr 180
	Trp Se	er Ser	Ile Ar 18		u Trj	p Th	r Se	r Pro 190	Th:	r Ph	e Gli	r. Tr	p Leu 195

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	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
5	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	Hıs	Tyr	Pro	Val 255
10	Glu	Val	Met	Leu	Lys 260										
	(2)	INFOR	RMAT	гои і	FOR S	SEQ :	ID NO	0:75	:						
15	(:	(<i>1</i>	A) LI B) Ti	ENGTI YPE :	CHARI H: 26 Amir DGY:	50 ar 10 Ad	mino cid		is						
	(x .	i) SI	EQUE	NCE I	DESC	RIPT	ION:	SEQ	ID 1	NO : 75	5:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
20	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
25	Asp	Thr	Tyr	His	туr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
30	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Gln	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Prc	Leu	His	Ala 135
35	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	As p	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165

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	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Glr 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
10	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 2 4 0
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
15	(2)	INFO	TAMS	I NO	FOR S	EQ :	ID NO	0:76	:						
20		() (I		ENGTH PE: OPOLO	H: 26 Amir DGY:	50 ar no Ad Line	mino cid ear	acio		NO : 76	ā:				
	1				5					10			Glu		15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	11e 25	Val	Gln	Ile	Leu	Ser 30
25	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val	Arg	Asp	Ser	His	7
										4 0					45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn		Asn	Gln	Asp	Ala	45
30					50					Leu 55			Asp Arg		45 Pro 60
30	Asp	Thr	Tyr	His	50 Tyr 65	Val	Val	Ser	Glu	Leu 55 Pro 70	Leu	Gly		Asn	45 Pro 60 Ser 75
30	Asp Tyr	Thr Lys	Tyr Glu	His Arg	50 Tyr 65 Tyr 80	Val Leu	Val Phe	Ser Val	Glu Tyr	Leu 55 Pro 70 Arg 85	Leu Pro	Gly Asp	Arg	Asn Val	45 Pro 60 Ser 75 Ser 90
3 0	Asp Tyr Ala	Thr Lys Val	Tyr Glu Asp	His Arg Ser	Tyr 65 Tyr 80 Tyr 95	Val Leu Tyr	Val Phe Tyr	Ser Val Asp	Glu Tyr Asp	Leu 555 Pro 70 Arg 85 Gly 100	Leu Pro Cys	Gly Asp Glu	Arg Gln	Asn Val Cys	45 Pro 60 Ser 75 Ser 90 Gly

											145					sp Va l
	Tyr	Leu	Asp	Val	Gln 155	Gl	u Ly	s Tr	p G	ly	Leu 160	Glu	ı As	p Va.	l Me	et Leu 165
5	Met	Gly	Asp	Phe	Asn 170	Ala	a Gly	ү Су	s S	er	Tyr 175	Val	Ar	g Pro	⊃ S∈	er Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	1 Trp	Th	r S	er	Pro 190	Thr	Phe	e Glr	ı Tr	p Leu 195
10	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Th	r Al	la :	Thr 205	Pro	Thi	His	Су	s Ala 210
	Tyr 7	Asp	Arg	Ile	Val 215	Val	Ala	Gly	γ Me	et 1	Leu 220	Leu	Arg	Gly	Al	a Val 225
	Val 1	Pro	Asp	Ser	Ala 230	Leu	Pro	Ph€	As	sn I	Phe 235	Gln	Ala	Ala	ту	r Gly 2 4 0
15	Leu S	Ser .	Asp	Gln	Leu 2 4 5	Ala	Gln	Ala	Il	e S	Ser .	Asp	His	Tyr	Pro	Val 255
	Glu V	al 1	1et		Lys 260											
	(2) IN	FORM	1ATI	ON F	or s	EQ]	D NO	D: 77	:							
20	(i)	(A)	LEI TYI	CE CI NGTH PE: 1 POLOG	: 26 Amin	o an	nino :id	CS: aci	ds							
	(xi)															
25	Leu Ly				_]	LO					15
	Met Se									2	! 5					30
30	Arg Ty				7 3					4	0					45
	Thr Al	a Va	al G	ly L	ys L 50	eu 1	Leu)	Asp	Asn	Le 5	u As 5	sn G	ln i	Asp A	Ala	Pro 60
	Asp Th	r T)	r H	is T	yr V. 85	al V	/al 9	Ser (Glu	Pr 7	0 Le	eu G	1y 1	Arg A	sn	Ser 75
35	Tyr Ly			,	30					8	5					Ser 90
	Ala Va	l As	p Se	er Ty	r T ₃ 95	r T	yr A	sp 1	Asp	Gl ₂	у Су Э	s G	lu P	ro C		Gly 105

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	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Trp	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
5	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met	Gly	Asp	Phe	As n	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200		Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
15	Tyr	Asp	Arg	Ile	Val		Ala	Gly	Met	Leu 220		Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	230		ı Pro	Phe	Asn	235		Ala	Ala	Tyr	Gly 240
20	Let	ı Sei	r Asp	Gl:	1 Let 24		a Glr	n Ala	a Ile	Ser 250		His	з Туг	Pro	255
	Glu	ı Va	l Mei	t Lei	26										
	(2)	INF	orma'	TION	FOR	SEQ	ID 1	NO : 71	B :						
25		(i)	(A) (B)	LENG TYPE	TH: : Am	260 ino	ERIS' amin Acid near								
	(xi)	SEQU	ENCE	DES	CRIF	тіои	: SE	Q ID	NO:	78:				
30	Le	u Ly 1	s Il	e Al	a Al	a Ph 5	e As	n Il	e Gl	n Th		e Gl	y Gl	u Th	r Lys 15
	Me	t S€	er As	n Al		r Le	eu Va	l Se	r Ty		e Va 5	l Gl	n Il	e Le	u Ser 30
	Ar	g Ty	yr As	sp Il		la Le 35	eu Va	ıl Gl	n Gl		1 Ar	g As	sp Se	er Hi	s Leu 45
35	Tì	nr Al	la Va	al G		ys Lo 50	eu Le	eu As	sp As		eu As	n Gl	ln As	sp Al	a Pro 60
	A	sp T	hr T	yr H		yr V 65	al Va	al Se	er Gl		:0 Le	eu Gl	ly A	rg As	sn Ser 75

	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Туг 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Tyr	11e 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	туг	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	As n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
25	Glu	Val	Met	Leu	Lys 260										
	(2)	INFOR	TAMS	ON I	FOR S	SEQ 1	ID NO	0:79	:						
30	()	(<i>)</i>	EQUEN A) LE B) TY O) TO	ENGTI PE :	Amir	0 an	nino cid		is						
	(x)	i) SE	EQUEN	ICE [DESC	RIPTI	ON:	SEQ	ID 1	10:79	e:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
35	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Asn	Leu 45

	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asr	Ser 75
5	туr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200		Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Туr	Asp	Arg	Ile	Val 215		Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	Asp	Ser	Ala 230		Pro	Phe	Asn	Phe 235		Ala	Ala	Tyr	Gly 240
	Lev	ser	r Asp	Glr.	Leu 245		Glr	Ala	Ile	Ser 250		His	Tyr	Pro	Val 255
30	Glu	ı Val	l Met	Lev	260										
	(2)	INF	ORMAT	NOIT	FOR	SEQ	ID N	10:80):						
35			SEQUE (A) I (B) I	LENG: TYPE	TH: I	260 a	amino Acid								
	(:	хı).	SEQUI	ENCE	DES	CRIP:	rion	: SE(Q ID	NO : 6	30:				
	Le	u Ly	s Ile	e Ala	a Ala	a Phe	e Ası	n Ile	e Glı	n Thi	r Phe	e Gly	/ Gl:	ı Th:	Lys
		-													

10

	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Туг	Ile 25		Gln	Ile	Leu	Se:
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40		Asp	Ser	His	Let
5	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Thr	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
10	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	11e 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	qzA	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

35 (2) INFORMATION FOR SEQ ID NO:81:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amine Acid
 - (D) TOPOLOGY: Linear

(xi)	SEQUENCE	DESCRIPTION:	SEQ :	ID	NO:81	.:			
		*1 51 - 1	T1 - /	a 1 -	- Th	Dho	Clar	0711	Th

	,		_								_,	c. 1	ca ?	m1- ·	T
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Glγ	ئادى	rnr	15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
10	Asp	Thr	Tyr	Asn	Tyr 65	Thr	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arc	g Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130		Pro	Leu	His	Ala 135
20	Ala	a Pro	o Gly	/ Asp	Ala 140	Val	Ala	Glu	lle	Asp 145		Leu	Туr	Asp	Val 150
	тy	r Le	u Asp	o Val	Gln 155		Lys	Trp	Gly	Leu 160		Asp	Val	. Met	Le u 165
25	Me	t Gl	y Asp	o Phe	170		Gly	Cys	s Ser	Tyr 175		Arg	Pro	Ser	Gln 180
	Tr	p Se	r Sei	r Ile	e Arg		ı Trp	Thi	r Sei	Pro 190		Phe	e Glr	1 Trp	195
	11	e Pr	o As	p Sei	r Ala 200		o Thr	Th:	r Ala	a Thi 209		Thi	His	s Cys	210
3 C	ту	r As	p Ar	g Il	e Val		l Ala	a Gl	y Me	t Lei 22		ı Arg	g Gl	y Ala	a Val 225
	Va	al Pr	o As	p Se	r Ala 230		u Pro	o Ph	e As	n Ph		n Ala	a Al	а Ту:	r Gly 240
35	Le	eu Se	er As	p Gl	n Lei 24		a Gl	n Al	a Il	e Se 25		p Hi	s Тү	r Pr	o Val 255
	G.	lu Vá	al Me	t Le	u Ly 26										

(2) INFORMATION FOR SEQ ID NO:82:

(1) SEQUENCE CHARACTERISTICS: (A) LENGTH 260 amino acids (B) TYPE: Amino Acid (D) TCPOLOGY: Linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82: 5 Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys 5 Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu 10 Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Asn Gln Asp Ala Pro Asp Thr Tyr His Asn Val Thr Ser Glu Pro Leu Gly Arg Asn Ser 15 Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser 20 115 Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 130 Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 25 140 Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Gln 170 30 Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Val 35 215 220 Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gly

Leu Ser Asp Glr. Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Val

245

Glu Val Met Leu Lys 260

5

(2) INFORMATION FOR SEQ ID NC:83:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 - (B) TYPE: Amino Acid
 - (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

10	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	туr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Asn	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	qeA	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
25	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
30	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Prc 190	Thr	Phe	Gln	Trp	Leu 195
35	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	Hıs	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225

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	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	туг	Pro	Val 255
5	Glu	Val	Met	Leu	Lys 260										
	(2)	INFC	TAMS	гои в	FOR S	SEQ :	ID NO	0:84	:						
	(:		EQUEN A) LI						ds						
10				PE: OPOLO											
	(x:	i) SI	EQUE	NCE I	DESC	RIPT	ON:	SEQ	ID 1	10 : 84	1 :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
15	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
20	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Asn	Ser	Thr	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
25	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	As n 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
3 C	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Prc	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	As p	Ala	Leu	Tyr	qeA	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
35	Met	Gly	Asp	Phe	As n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Prc 190	Thr	Phe	Gln	Trp	Leu 195

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	lle Pro	qaA	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Суз	Ala 210
	Tyr Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
5	Val Pro	As p	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	тут	Gly 240
	Leu Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
10	Glu Val	Met	Leu	Lys 260										
	(2) INFO	RMAT:	ION I	FOR S	SEQ I	ID NO	0:85	:						
15	(. (EQUEN A) LI B) TY D) TO	ENGTH YPE :	H: 26 Amir	60 ar	mino cid		is						
	(xi) S	EQUE	VCE I	DESCI	RIPT	ION:	SEQ	ID 1	10 : 8 :	5 :				
	Leu Lys 1	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
20	Met Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Le u 4 5
	Thr Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
25	Asp Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
30	Ala Val	Asp	Asn	Tyr 95	Thr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
35	Ala Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Glγ	Leu 160	Glu	Asp	Val	Met	Leu 165

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	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
10	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	туr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
15	(2)	INFO	TAMS	I NOI	FOR S	SEQ :	ID NO	0:86	:						
	(:	() (I	EQUEN A) LE B) TY	ENGTI PE:	H: 26 Amir	50 ar 10 Ad	mino cid		is						
20	(x:	i) SI	EQUE	VCE I	DESC	RIPT	: NO	SEQ	ID i	10:86	5 :				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
25	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Glu	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
30	Asp	Thr	туr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
35	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120

	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
5	Met	Gly	Asp	Phe	As n 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT:	ION :	FOR S	SEQ	ID N	O:B7	:						
20	(:	(:		ENGT: YPE :		60 ai	mino cid		ds						
	(x	i) S	EQUEI	NCE :	DESC	RIPT	ION:	SEQ	ID	NO : 8	7:				
25	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
30	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	_	Asp	Ser	Hıs	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55		Gln	Asp	Ala	Pro 6C
	Asp	Thr	Tyr	His	Glu 65		Val	Ser	Glu	Pro 70		Gly	Arg	Asn	Ser 75
35	Tyr	Lys	Glu	Arg	Tyr 80		Phe	val	Tyr	Arg 85		Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	-	Tyr	Asp	Asp	Gly 100	_	Glu	Pro	Cys	Gly 105

Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser

					110					115		5			120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala
5	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
15	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
20	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT:	ION I	FOR S	SEQ :	ID NO	0:88	:						
25	(:	(1	A) LI B) TY		H: 2€ Amir	50 ar 10 Ad			ds						
	(x:	i) SI	EQUE	VCE I	DESC	RIPT	: NO	SEQ	ID 1	10 : 8 8	3:				
30	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	Ala	Leu 45
35	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Arg	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Ala 65	Val	Val	Ser	Arg	Pro 70	Leu	Gly	Arg	Asn	Ser 75

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	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
5	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e 130	Val	Pro	Leu	Hıs	Ala 135
10	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	туr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	qaA	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
25	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT	ION	FOR	SEQ	ID N	0:89	:						
30	((B) T	ENGT YPE :		60 a no A	mino cid		ds						
	(x	i) S	EQUE	NCE	DESC	RIPT	ION:	SEQ	ID	NO : 8	9 :				
	Leu 1	-	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr		Gly	Glu	Thr	Lys 15
35	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25		Gln	Ile	Leu	Ser 30
	Arg	Туг	Asp	Ile	Ala		Val	Gln	Glu	Val	_	Asp	Ser	His	Leu 45

	Thr	Ala	Arg	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	naA	Ser 75
5	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	qeA	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
10	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
15	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
20	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
25	Val	Pro	qeA	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	туг	Pro	Val 255
30	Glu	Val	Met	Leu	Lys 260										
	(2)		RMAT:						:						
35	ν.	() {1	A) Li B) T' D) T(ENGTI PE :	H: 26 Amir	50 ar 10 Ad	mino cid		ds						
	(x	i) si	EQUE	1CE I	DESCI	RIPT:	100:	SEQ	ID 1	10 ; 9 (.				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15

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	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
5	Thr	Ala	Val	Gly	Lys 50	Leu	Asn	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
10	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
15	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	Hıs	Ala 135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Va l
20	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
25	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	туr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
30	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

- 35 (2) INFORMATION FOR SEQ ID NO:91:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 260 amino acids
 (B) TYPE: Amino Acid

 - (D) TOPOLOGY: Linear

(xi)	SEQUENCE	DESCRIPTION:	SEO	ID	NO:91 -
------	----------	--------------	-----	----	---------

	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr	Phe	Gly	Glu	Thr	Lys 15
5	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Arg	Asp	Asn	Leu 55	Asn	Gln	Asp	Ala	Prc 60
10	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
15	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	11e 130	Val	Pro	Leu	Hıs	Ala 135
20	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
25	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
30	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
35	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										

(2) INFORMATION FOR SEQ ID NO:92:

WO 96/26279

	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 260 amino acids(B) TYPE: Amino Acid(D) TOPOLOGY: Linear	
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:	
	Leu Lys Ile Ala Ala Phe Asn Ile Gln Thr Phe Gly Glu Thr Lys 1 5 10 15	
	Met Ser Asn Ala Thr Leu Val Ser Tyr Ile Val Gln Ile Leu Ser 20 25 30	
10	Arg Tyr Asp Ile Ala Leu Val Gln Glu Val Arg Asp Ser His Leu 35 40 45	
	Thr Ala Val Gly Lys Leu Leu Asp Asn Leu Cys Gln Asp Ala Pro 50 55 60	
15	Asp Thr Tyr His Tyr Val Val Ser Glu Pro Leu Gly Arg Asn Ser 65 70 75	
	Tyr Lys Glu Arg Tyr Leu Phe Val Tyr Arg Pro Asp Gln Val Ser 80 85 90	
	Ala Val Asp Ser Tyr Tyr Tyr Asp Asp Gly Cys Glu Pro Cys Gly 95 100 105	
20	Asn Asp Thr Phe Asn Arg Glu Pro Ala Ile Val Arg Phe Phe Ser 110 115 120	
	Arg Phe Thr Glu Val Arg Glu Phe Ala Ile Val Pro Leu His Ala 125 130 135	
25	Ala Pro Gly Asp Ala Val Ala Glu Ile Asp Ala Leu Tyr Asp Val 140 145 150	
	Tyr Leu Asp Val Gln Glu Lys Trp Gly Leu Glu Asp Val Met Leu 155 160 165	
	Met Gly Asp Phe Asn Ala Gly Cys Ser Tyr Val Arg Pro Ser Glr 170 175 180	i)
30	Trp Ser Ser Ile Arg Leu Trp Thr Ser Pro Thr Phe Gln Trp Leu 185 190 199	5
	Ile Pro Asp Ser Ala Asp Thr Thr Ala Thr Pro Thr His Cys Ala 200 205 21	E C
35	Tyr Asp Arg Ile Val Val Ala Gly Met Leu Leu Arg Gly Ala Va 215 220 22	1 5
	Val Pro Asp Ser Ala Leu Pro Phe Asn Phe Gln Ala Ala Tyr Gl 230 235 24	У О
	Leu Ser Asp Gln Leu Ala Gln Ala Ile Ser Asp His Tyr Pro Va 245 250 25	1 5

Glu Val Met Leu Lys 260

5

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 260 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

	,	-, -	202		2250	KIFI	TON:	SEQ	10	NO:9	3:				
10	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
15	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Phe	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
20			Glu		80					85					90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
			Thr		110					115					120
25			Thr		125					130					135
			Gly		140					145					150
30			Asp		155					160					165
			Asp		170					175					180
			Ser		185					190					195
35			Asp		200					205					210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225

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	Val P	rc A	Asp S		la L 30	eu F	ro F	he A		Phe (Gln	Ala	Ala		Gly 2 4 0
	Leu S	er A	Asp (eu A :45	la C	Sln 🎜	Ala		Ser 250	Asp	His	Tyr		Val 255
5	Glu V	/al M	Met 1		260 260										
	(2) II	1FORI	MATI	ON FO	OR SE	EQ II	ON C	: 94 :							
LO	(i)	(A (B) LE	CE CH NGTH PE: 1 POLO	: 260 Amino	am: Ac:	ino d id		.s						
	(xi) SE	QUEN	CE D	ESCR	IPTI	: NC	SEQ	ID 1	10 : 94	.:				
	Leu :	Lys	Ile	Ala .	Ala 1	Phe .	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
15	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
20	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Le u 5 5	Lys	Gln	Asp	Ala	Pro 60
	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
25	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100		Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	11e		Arg	Phe	Phe	Ser 120
30	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130		Pro	Leu	His	135
	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	ı Ile	2 Asp 145		a Lev	туг	Asp	Val 150
	Tyr	Leu	ı Asp	Val	Gln 155	Glu	Lys	Trp	Gly	y Let 160		Asp	o Val	l Met	165
35	Met	Gly	/ Asp) Phe	As n 170		Gly	Cys	s Se	r Ty:		l Arg	g Pro	o Sei	r Glr 180
	Trp	Sei	r Sei	: Ile	Arg		Trp	Th:	r Se	r Pro		r Ph	e Gl:	n Trj	p Let 195

	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
5	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Tyr	Pro	Val 255
10	Glu	Val	Met	Leu	Lys 260										
	(2)	INFO	RMAT:	ION I	FOR S	SEQ :	ID NO	0:95	:						
15	((1	EQUERA) LI B) To	ENGTI YPE :	H: 26 Amir	50 an 10 Ad	mino cid		is						
	(x	i) SI	EQUE	VCE I	DESC	RIPT	ION:	SEQ	ID 1	10 : 9 !	5:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
20	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Arg	Gln	Asp	Ala	Pro 60
25	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	Ser 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
30	Ala	Val	Asp	Ser	Туr 95	Tyr	туг	Asp	Asp	Gly 100	Cys	Glu	Pro	Cys	Gly 105
	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
35	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165

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	Met	Gly	Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
5	Ile	Pro	Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	туг	Asp	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
10	Val	Pro	Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	His	Туг	Pro	Val 255
	Glu	Val	Met	Leu	Lys 260										
15	(2)	INFO	TAMS	ON I	FOR S	SEQ I	ID NO	0:96	:						
	(:	()	EQUEN A) LE B) TY	ENGTI YPE :	H: 26 Amir	50 ar 10 Ac	mino cid		is						
20	(x:	i) S1	EQUE	NCE I	DESCI	RIPT	ION:	SEQ	ID 1	NO : 9	6:				
	Leu 1	Lys	Ile	Ala	Ala 5	Phe	Asn	Ile	Gln	Thr 10	Phe	Gly	Glu	Thr	Lys 15
	Met	Ser	Asn	Ala	Thr 20	Leu	Val	Ser	Tyr	Ile 25	Val	Gln	Ile	Leu	Ser 30
25	Arg	Tyr	Asp	Ile	Ala 35	Leu	Val	Gln	Glu	Val 40	Arg	Asp	Ser	His	Leu 45
	Thr	Ala	Val	Gly	Lys 50	Leu	Leu	Asp	Asn	Leu 55	Trp	Gln	Asp	Ala	Pro 60
3 C	Asp	Thr	Tyr	His	Tyr 65	Val	Val	Ser	Glu	Pro 70	Leu	Gly	Arg	Asn	S e r 75
	Tyr	Lys	Glu	Arg	Tyr 80	Leu	Phe	Val	Tyr	Arg 85	Pro	Asp	Gln	Val	Ser 90
	Ala	Val	Asp	Ser	Tyr 95	Tyr	Tyr	Asp	Asp	Gly 100	-	Glu	Pro	Cys	Gly 105
35	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115		Arg	Phe	Phe	Ser 120

	Ala Pr	o Gly	Asp	Ala 140	Val	Ala	Glu	Ile	As p 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr Le	eu Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
5	Met Gl	ly Asp	Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp Se	er Ser	Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
10	Ile Pi	ro Asp	Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
	Tyr As	sp Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val P	ro Asp	Ser	Ala 230	Leu	Pro	Phe	Asn	Phe 235	Gln	Ala	Ala	Tyr	Gly 240
15	Leu S	er Asp	Gln	Leu 245	Ala	Gln	Ala	Ile	Ser 250	Asp	Hıs	Tyr	Pro	Val 255
	Glu V	al Met	Leu	Lys 260										
	(2) IN	FORMAT	'ION	FOR S	SEQ :	ID N	0:97	:						
20	(i)	SEQUE	NCE	~*** D :	COR									
		(A) I (B) T		H: 20 Amin	60 ai	mino cid		ds						
		(A) I (B) T	ENGT TYPE : TOPOL	H: 20 Amii OGY:	60 an no A Lin	mino cid ear	aci		N O : 9	7:				
25	(xi)	(A) I (B) T (D) T	ENGT: TYPE: TOPOL	H: 20 Amin OGY: DESC	60 ai no A Lin	mino cid ear ION:	acio SEQ	ID:		Phe	Gly	Glu	Thr	Lys 15
25	(xi) Leu L 1	(A) I (B) T (D) T	ENGT: TYPE: TOPOL ENCE Ala	H: 20 Amin OGY: DESCI Ala 5	60 amno A Lin RIPT	mino cid ear ION:	SEQ	ID :	Thr 10	Phe Val				15
25	(xi) Leu L 1 Met S	(A) I (B) T (D) T SEQUE	ENGT: COPOL CNCE Ala	H: 20 Amin OGY: DESCI Ala 5 Thr 20	60 anno A Lin RIPT Phe Leu	mino cid ear ION: Asn Val	SEQ Ile	ID : Gln Tyr	Thr 10 Ile 25	Phe Val	Gln	Ile	Leu	15 ser 30
	(xi) Leu L 1 Met S	(A) I (B) T (D) T SEQUE TYS Ile	ENGT: TYPE: TOPOL ENCE Ala Ala Dile	H: 20 Amin OGY: DESCI Ala 5 Thr 20 Ala 35	60 aino A Lin RIPT Phe Leu Leu	mino cid ear ION: Asn Val	SEQ Ile Ser	ID : Gln Tyr Glu	Thr 10 Ile 25 Val 40	Phe Val Arg	Gln Asp	Ile Ser	Leu His	15 Ser 30 Leu 45
	(xi) Leu L 1 Met S Arg T	(A) I (B) T (D) T SEQUE SYS Ile	ENGT: TYPE: TOPOL ENCE Ala Ala I Ala I Gly	H: 20 Amin OGY: DESCI Ala 5 Thr 20 Ala 35 Lys 50	60 aino A Lin RIPT Phe Leu Leu Leu Val	mino cid ear ION: Asn Val Val	SEQ Ile Ser Gln	ID : Gln Tyr Glu Asn	Thr 10 Ile 25 Val 40 Leu 55	Phe Val	Gln Asp Gln	Ile Ser	Leu His	15 Ser 30 Leu 45 Pro 60
	(xi) Leu L 1 Met S Arg T Thr A	(A) I (B) T (D) T SEQUE SYS Ile (er Ass	ENGT: TYPE: TOPOL ENCE Ala Ala I Ala I Gly THIS	H: 20 Amin OGY: DESC! Ala 5 Thr 20 Ala 35 Lys 50 65	60 aino A Lin RIPT Phe Leu Leu Val	mino cid ear ION: Asn Val Val	SEQ Ile Ser Gln Asp	ID : Gln Tyr Glu Asn	Thr 10 1le 25 Val 40 Leu 55	Phe Val Arg	Gln Asp Gln	Ile Ser Asp	Leu His Ala Asn	15 Ser 30 Leu 45 Pro 60 Ser 75

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	Asn	Asp	Thr	Phe	Asn 110	Arg	Glu	Pro	Ala	Ile 115	Val	Arg	Phe	Phe	Ser 120
	Arg	Phe	Thr	Glu	Val 125	Arg	Glu	Phe	Ala	Ile 130	Val	Pro	Leu	His	Ala 135
5	Ala	Pro	Gly	Asp	Ala 140	Val	Ala	Glu	Ile	Asp 145	Ala	Leu	Tyr	Asp	Val 150
	Tyr	Leu	Asp	Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
10	Met	Gly	Asp	Phe	As n	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
	Trp	Ser	Ser	Ile	Arg 185		Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp	Ser	Ala 200		Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
15	Tyr	Asp	Arg	Ile	Val 215		Ala	Gly	/ Met	220		Arg	g Gly	/ Ala	Val 225
	Val	Pro	Asp	Ser	230		ı Pro) Phe	e Ası	n Phe 23!	e Glr 5	n Ala	a Ala	а Туз	Gly 240
20	Lev	ı Se:	r Ası	Glr	1 Let 24!		a Gli	n Ala	a Ile	e Se: 25	r Asp	His	з Ту	r Pro	255
	G11	ı Va	l Me	t Lev	1 Ly:										
	(2)	INF	orma	TION	FOR	SEQ	ID	N O : 9	8 :						
25		(i)	(B)	ENCE LENG TYPE TOPO	TH: : Am	260 ino	amin Acid	o ac	: ids						
	(xi)	SEQU	ENCE	DES	CRIF	AOIT	r: SE	Q II	NO:	98:				
30	Le	u Ly 1	/s Il	e Al	a Al	a Ph 5	ne As	in Il	e Gl		nr Ph	e Gl	y Gl	u Th	r Lys 15
	Me	et S€	er As	sn Al		nr Le 20	eu Va	al Se	er Ty	yr I	le Va 25	al Gl	ln Il	le Le	eu Ser 30
	A	rg T	yr A:	sp I		la Le 35	eu V	al G	ln G	lu V	al Az 40	rg As	sp Se	er H	ıs Leu 45
35	T	hr A	la V	al G		ys L 50	eu L	eu A	sp A	sn L	eu A:	sn G	ln A	sp A	la Pro 60
	A	sp T	hr T	yr H		yr V 65	al V	al A	sn G	lu T	hr L 70	eu G	ly A	rg A	sn Ser 75

-128-

										8 5	5				l Ser 90
					,	,				100	3				5 Gly 105
5				ir Ph	110					115	5				120
				ır Glı	125					130	1				135
10				y Asp	110					145					150
	Tyr	Le	u As	p Val	Gln 155	Glu	Lys	Trp	Gly	Leu 160	Glu	Asp	Val	Met	Leu 165
	Met	Gl:	y As	p Phe	Asn 170	Ala	Gly	Cys	Ser	Tyr 175	Val	Arg	Pro	Ser	Gln 180
15	Trp	Ser	r Se:	r Ile	Arg 185	Leu	Trp	Thr	Ser	Pro 190	Thr	Phe	Gln	Trp	Leu 195
	Ile	Pro	Asp) Ser	Ala 200	Asp	Thr	Thr	Ala	Thr 205	Pro	Thr	His	Cys	Ala 210
20	Tyr	qeA	Arg	Ile	Val 215	Val	Ala	Gly	Met	Leu 220	Leu	Arg	Gly	Ala	Val 225
	Val	Pro	Asp	Ser	Ala 230	Leu :	Pro	Phe	Asn	Phe 235	Gln	Ala .	Ala	Tyr	Gly 240
	Leu	Ser	Asp	Gln	Leu . 245	Ala	Gln .	Ala	Ile	Ser 250	Asp	His '	Tyr		Val 255
25	Glu	Val	Met	Leu	Lys 260										

Claims

What is claimed is

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- 1. A human DNase I actin-resistant variant.
- 2. A variant of claim 1 that has a binding affinity for actin that is at least five-fold less than that of native human DNase I. 5
 - 3. A variant of claim 1 that has a binding affinity for actin that is at least 100-fold less than that of native human DNase I.
 - 4. A variant of claim 1 comprising an amino acid sequence having at least 90% identity with the amino acid sequence of native human DNase 1 shown in Figure 1.
 - 5. A variant of claim 1 comprising an amino acid sequence having at least 95% identity with the amino acid sequence of native human DNase I shown in Figure 1.
 - 6. A human DNase I actin-resistant variant having an amino acid sequence that differs from the amino acid sequence shown in Figure 1 by the substitution of one amino acid for another at only a single position within the Figure 1 sequence.
 - 7. A variant of claim 6 wherein the amino acid substitution creates a glycosylation site within the variant that is not present in native human DNase I.
 - 8. A variant of claim 6 wherein the amino acid substitution is at one of the following positions within the Figure 1 sequence: His44, Leu45, Val48, Gly49, Leu52, Asp53, Asn56, His64, Tyr65, Val66, Val67, Ser68. Glu69, or Alal 14.
 - 9. A human DNase I actin-resistant variant having an amino acid sequence that differs from the amino acid sequence shown in Figure 1 by the substitution of one amino acid for another at two or more positions within the Figure 1 sequence.
 - 10. A variant of claim 9 wherein at least one of the amino acid substitutions is made at one of the following positions within the Figure 1 sequence: His44, Leu45, Val48, Gly49, Leu52, Asp53, Asn56, His64, Tyr65, Val66, Val67, Ser68, Glu69, Ser94, Tyr96, or Ala114.
 - 11. A variant of claim 9 wherein at least one of the amino acid substitutions creates a glycosylation site within the variant that is not present in native human DNase I.
 - 12. An isolated nucleic acid encoding a human DNase I actin-resistant variant.
 - 13. The nucleic acid of claim 12 comprising a nucleotide sequence that encodes an amino acid sequence having at least 90% identity with the amino acid sequence of native human DNase shown in Figure 1.
 - 14. The nucleic acid of claim 12 comprising a nucleotide sequence that encodes an amino acid sequence having at least 95% identity with the amino acid sequence of native human DNase shown in Figure ı
 - 15 The nucleic acid of claim 12 comprising a nucleotide sequence that encodes an amino acid sequence that differs from the amino acid sequence shown in Figure 1 by the substitution of one amino acid for 35 another at only a single position within the Figure 1 sequence

16. The nucleic acid of claim 12 comprising a nucleotide sequence that encodes an amino acid sequence that differs from the amino acid sequence shown in Figure 1 by the substitution of one amino acid for another at only two positions within the Figure 1 sequence.

- 17. A method for the treatment of a patient having a pulmonary disease or disorder comprising administering to the patient a therapeutically effective amount of an actin-resistant variant of human DNase I
 - 18. The method of claim 17 wherein the disease or disorder is cystic fibrosis.

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- 19. The method of claim 17 wherein the disease or disorder is chronic bronchitis.
- 20. A pharmaceutical composition comprising an actin-resistant variant of human DNase I and optionally a pharmaceutically acceptable excipient.
 - 21. The composition of claim 20 wherein the composition is in liquid form.
 - 22. The composition of claim 21 wherein the composition is in powder form.

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LKIAAFNIQTFGETKMSNATLVSYIVQILSRYDIALVQEVRDSHLTAVGK LLDNLNQDAPDTYHYVVSEPLGRNSYKERYLFVYRPDQVSAVDSYYYDDG CEPCGNDTFNREPAIVRFFSRFTEVREFAIVPLHAAPGDAVAEIDALYDV YLDVQEKWGLEDVMLMGDFNAGCSYVRPSQWSSIRLWTSPTFQWLIPDSA DTTATPTHCAYDRIVVAGMLLRGAVVPDSALPFNFQAAYGLSDQLAQAIS DHYPVEVMLK

FIG. 1

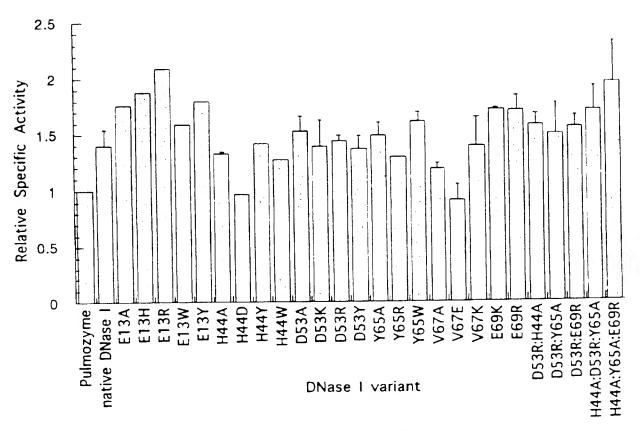


FIG. 2A

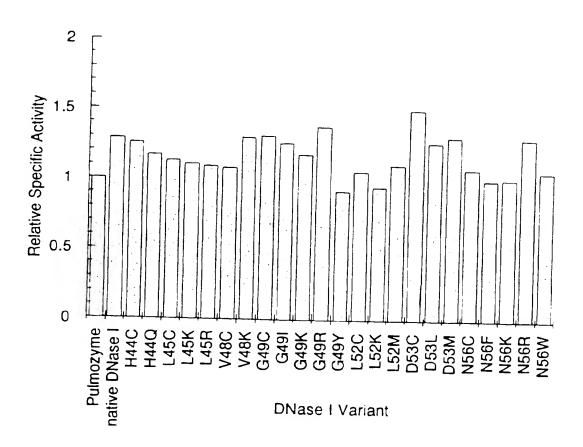


FIG. 2B

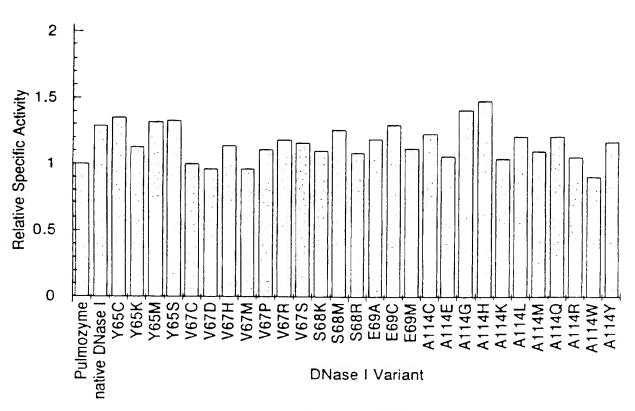
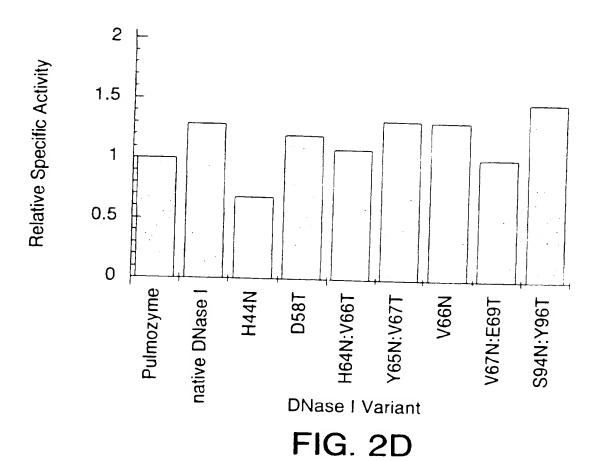
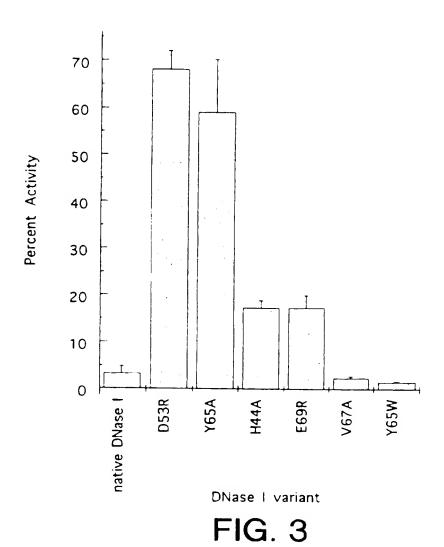


FIG. 2C



SUBSTITUTE SHEET (RULE 26)



SUBSTITUTE SHEET (RULE 26)

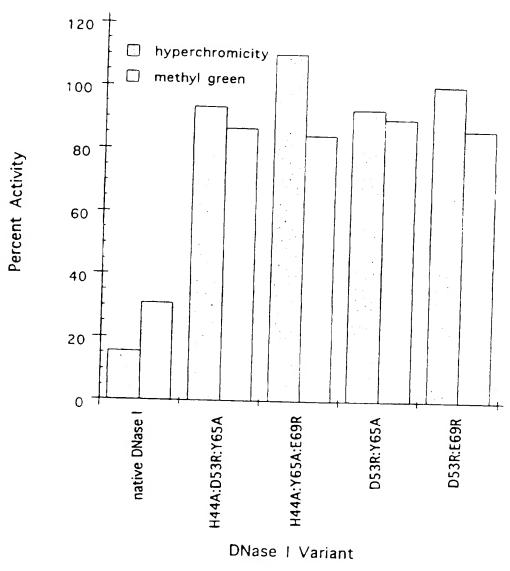


FIG. 4

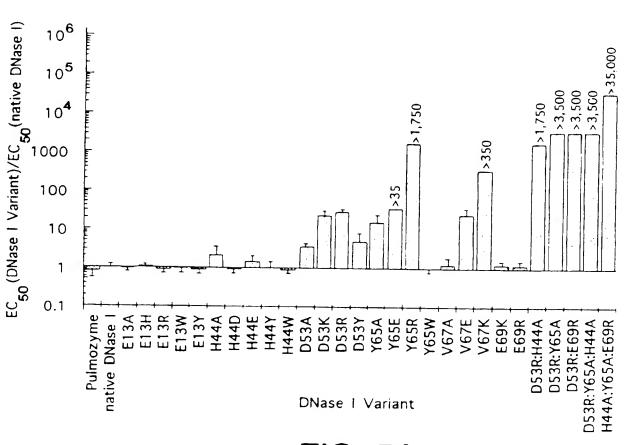


FIG. 5A

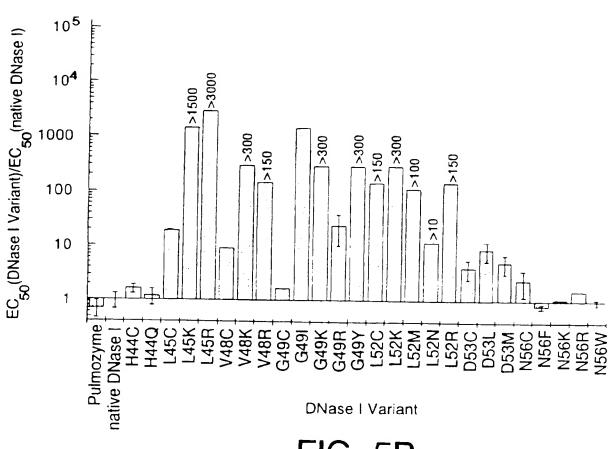


FIG. 5B

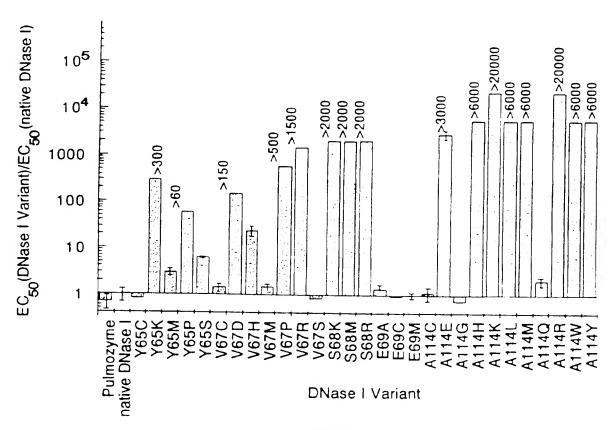


FIG. 5C

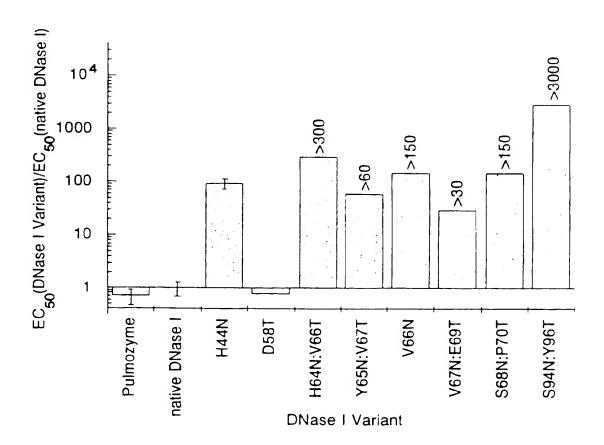


FIG. 5D

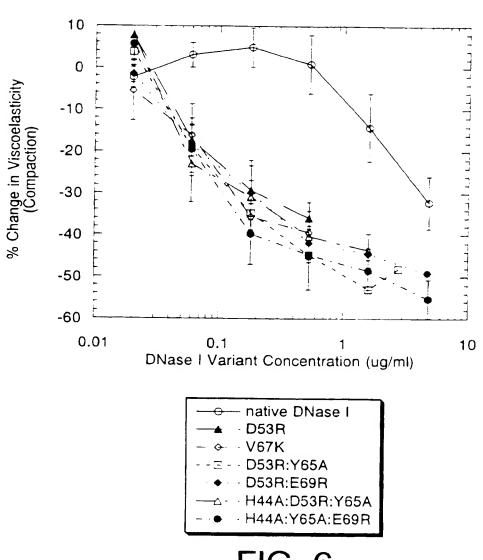


FIG. 6

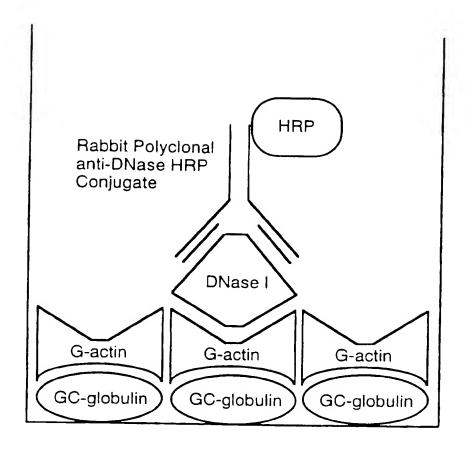


FIG. 7

INTERNATIONAL SEARCH REPORT

Internation Application No.

PCT/US 96/02421 A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C12N15/55 C12N9/22 A61K38/46 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) C12N A61K IPC 6 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Category ' Citation of document, with indication, where appropriate, of the relevant passages WO,A,90 07572 (GENENTECH INC) 12 July 1990 1,4-7,9, Χ 11-22 cited in the application see page 3, line 19 - page 6, line 25 see page 16, line 32 - page 17, line 34 see example 5 Y see claims 1,4-7,9,11-22 WO,A,94 22465 (BRIGHAM & WOMENS HOSPITAL) 1,4-7,9, Υ 13 October 1994 11-22 cited in the application see page 7 see page 11, line 7 - page 15, line 28 see examples 4.5 -/--Х Further documents are listed in the continuation of box C. Х Patent family members are listed in annex. Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date "L." document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified). involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled other means document published prior to the international filing date but later than the priority date claimed. "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 25.07.96 18 July 1996 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,

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